AN INVESTIGATION INTO THE USE OF ULTRASOUND IN THE SYNTHESIS OF FINE CHEMICALS

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A thesis submitted in partial fulfilment of the requirements of the University of Abertay Dundee for the degree of Doctor of Philosophy

This research programme was carried out in collaboration with Synthetic Chemicals Limited, Four Ashes, Wolverhampton.

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I certify that this thesis is the true and accurate version of the thesis approved by the examiners.

Signed [redacted] Date 1/6/95

(Director of Studies)

This Thesis is dedicated to my mother, Beatrice,
and to the memory of my late father, "Rab".C

DECLARATION

I hereby declare that the work presented in this thesis was carried out by me at the University of Abertay Dundee and at Synthetic Chemicals Limited, Four Ashes, Wolverhampton except where due acknowledgement is made, and has not been submitted by me for any other degree.

Signed: 

Date: 31/5/95

CONTENTS

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Finally I would like to thank my girlfriend, Sharon for her support and humour throughout the inevitable "highs and lows" that are associated with research work.

ABSTRACT

The application of ultrasound to the oxidative dimerisation of pivalic acid to tetramethyladipic acid (TMAA; 2,2,4,4-tetramethylhexa-1,6-dioic acid) using Fenton's reagent is described. Various parameters of the reaction were investigated (gas, equivalents of reagents, temperature, and sonication) and their effect on the yield of TMAA is discussed. Separation of the reaction mixture into TMAA (dimer) and the trimers and tetramers was achieved. The reaction conditions were optimised using experimental design, and statistical analysis illustrates the significant factors that affect the yield. Optimal reaction conditions for the production of TMAA were found to be 0.17 equivalents of Fenton's reagent, high dilution no ultrasound, under nitrogen.

Alternative sources of hydroxyl radicals in organic solvents were also investigated

The production of 3-bromothiophene (3BT) from the rearrangement of 2,5-dibromothiophene and reduction of 2,3,5-tribromothiophene was investigated. Ultrasound, reaction time and temperature all have an effect on the yield and selectivity in the synthesis of 3BT.

Ultrasound was found to have a modest effect on the yield of 2-methoxythiophene from 2-bromthiophene using sodium methoxide with several catalyst systems (Cu, CuO, CuO/KI, CuO/KI/Copper acetyl acetonate).

2-Bromothiophene was used as a substrate in attempted Wurtz-type coupling reaction conditions. These reactions produced complex mixtures of bromothiophenes via halogen rearrangements.

The silylation of bromothiophenes was successfully achieved using several bromothiophene substrates under quiet and sonicated conditions with various reaction times and equivalents of reagents.

A calorimetry study on the acoustic output of the ultrasonic probe provided data at different temperatures, depths, solvents, and power settings. The resultant data was in strong agreement with previously published work.

FOREWORD

Bracketed arabic numerals in the text refer to the diagrams of the molecular formulae, Arabic superscripts indicate references.

The abbreviations below have been used in the text.

Ac	acetyl group CH_3CO
bp	boiling point
DMF	N,N-dimethylformamide
DMSO	dimethylsulphoxide
Et	ethyl group
EtOH	ethanol
FTIR	Fourier transform infra-red specroscopy
LDA	lithium diisopropylamide
Me	methyl group
MeOH	methanol
mp	melting point
nmr	nuclear magnetic resonance
Ph	phenyl group
pmr	proton magnetic rersonance
THF	tetrahydrofuran
TMAA	tetramethyladipic acid or 2,2,4,4-tetramethylhexa-1,6-dioic acid
tlc	thin layer chromatography
Ts	*para*-toluenesulfonyl chloride
US	ultrasound
uv	ultraviolet

1.0 INTRODUCTION

1.0 INTRODUCTION

The aim of this introduction is to provide a background to the origin of ultrasound, the theory of cavitation, and the application of ultrasound in chemistry (sonochemistry) with particular interest paid to organic synthesis. Reviews in sonochemistry are numerous[1-6] and can be consulted for a more comprehensive background on sonochemistry.

General

Ultrasound is sound frequency outwith the audible range (16Hz-18kHz) of the human ear, but it is the range from 20kHz to 2MHz that has been shown to have an effect on many chemical reactions. This is referred to as high power ultrasound which can achieve permanent chemical or physical change in a substance. The power densities obtained range from 1-1000's of Wcm^{-2} which cause an effect known as cavitation and microstreaming within liquids, heating and fatigue in solids, and surface instability effects[7] at liquid-liquid and liquid-gas interfaces. These physical effects are used to advantage in many areas as illustrated in Table 1.1:

Table 1.1 Ultrasound Applications

Biology	Homogenisation, cell disruption.
Engineering	Soldering, welding, fatigue testing, drilling.
Geology	Echo ranging, depth finding, oil & mineral exploration.
Industrial	Filtration, crystallisation, degassing, degreasing, emulsification.
Medicine	Imaging, physiotherapy, dental descaling.
Physics	Cavitation, wave phenomena, solvent studies.
Polymers	Polymerisation, depolymerisation, molecular weight degradation.
Chemistry	Reagent dispersion, mass transport, surface cleaning, rate and yield enhancement

Some of the above applications use low power "high frequency" ultrasound which is in the frequency range 2-10MHz. This type of ultrasound is used generally for diagnostic purposes of imaging, and non-destructive, non-invasive testing. Practical applications are foetal scanning, and metallurgical purposes such as weld inspection and thickness measurement.

History

In the 19th century (1894) the destroyer H.M.S. Daring inexplicably failed to meet its specifications i.e. its speed and efficiency were far lower than that for which it was designed. Thornycroft and Barnaby[8] observed severe slippage and vibration from the ship's screw propeller. By increasing the surface area and decreasing the angular velocity of the propeller the problem was solved. Thornycroft and Barnaby's details of bubble formation from the moving propeller was the first description of cavitation, which occurs during turbulent flow and ultrasonic irradiation of liquids, and is still an erosion problem on screw propellers of modern-day ships and submarines. Lord Rayleigh[9] produced the first mathematical models for the collapse of cavities within incompressible liquids. He predicted colossal localised temperatures (10,000 K) and pressures (10,000 atm) during such violent collapse.

Paul Langevin was the first person to transmit sound waves in sea water[10] which it is said[6] arose out of a competition in 1912 to find a method of detecting icebergs. However the first practical application was to detect submarines after the casualties inflicted during the First World War. Langevin employed the piezoelectric effect by sandwiching quartz crystals between steel plates to produce the first underwater sound transducer. The piezoelectric effect was discovered by Pierre and Jacques Curie[11] who found that when stress was applied to Rochelle salt (SiO_2) an electric charge was produced, and conversely when an electric charge was applied to the salt, a change in dimension resulted.

The first chemical[12] and biological[13] effects were reported by Loomis in 1927. The remarkable effects of ultrasound, such as the heating of solids and liquids, formation of fogs and emulsions were reported and, more importantly, they observed effects caused not just by heating. The iodine clock reaction was found to be accelerated when ultrasound was applied to the system. In this same paper were reported the astounding effects on small animals: "small fish and frogs are killed by exposure of one or two minutes", and they also found "mice are less sensitive, a twenty minute exposure not resulting in death, though at the end of the treatment the animal was barely able to move"! Loomis also reported that 300kHz ultrasound destroys nitrogen tri-iodide and other unstable substances, accelerates several chemical reactions and expels gases from liquids. Although these discoveries were over 65 years ago relatively few papers were published[14-19] up to the mid 1970s. The application of ultrasound to chemistry did not advance significantly until cheap and reliable ultrasonic cleaning baths and ultrasonic probes were available in the 1970s.

1.1 EQUIPMENT

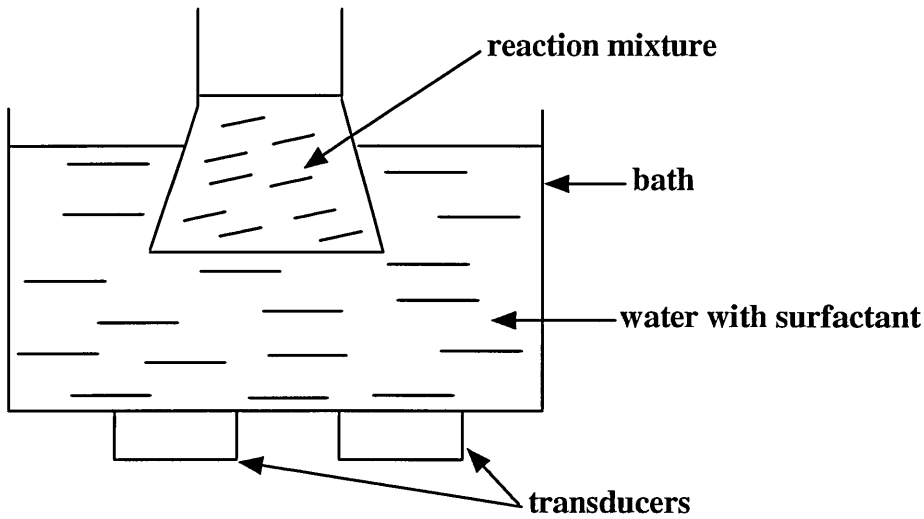
Laboratory

In the laboratory there are three common types of equipment available for experimental work: the ultrasonic cleaning bath, the ultrasonic probe and the sonic cup horn which is bolted onto the probe of an ultrasonic generator. In all these cases the ultimate source of the ultrasound waves comes from a piezoelectric crystal which was discussed[11] earlier. Other equipment is available and it is discussed[20] in the literature.

Ultrasonic Cleaning Bath

It is the ultrasonic (US) cleaning bath [Figure 1.1] that has provided most chemists with a convenient and cheap method of introduction into the area of sonochemistry. These US cleaning baths are widely available and many laboratories have them anyway for cleaning purposes. The bath itself is sonicated using transducers bonded directly to the floor of the bath and these emit ultrasound which produces cavitation within the bath.

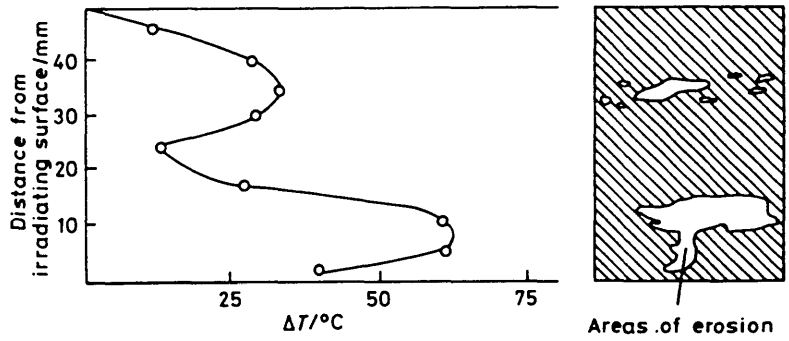
Figure 1.1 Ultrasonic Cleaning Bath



To sonicate a sample it must be contained in a vessel which is immersed into the ultrasonic bath, where the ultrasound is transmitted into the solution itself. Using a flat bottomed flask aids this process. The bath is limited in its use since the amount of power obtained from it is not easily measured and reproducibility is a problem. Indeed the power varies from bath to bath and even with the age of equipment. The position of the vessel within the bath is also critical and must be chosen carefully

between experiments to obtain optimum results. The control of temperature is not easy with a bath either, and Suslick[3] has cautioned the use of the US cleaning bath as an apparatus of limited capability. However the optimum cavitation position can be found by using a simple frame covered with aluminium foil, which is perforated when subjected to cavitation. Pugin[21] has compared the cavitation effects on a piece of aluminium foil immersed in a bath and temperature attained as a function of distance from the bath bottom [Figure 1.2].

Figure 1.2 Aluminium Foil Jig in US Cleaning Bath[21]

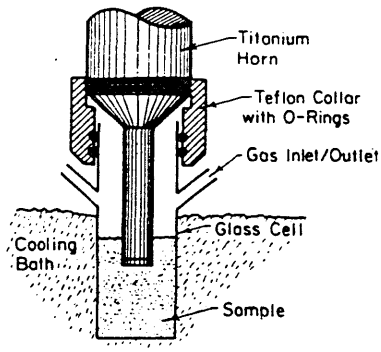


This simple experiment illustrates clearly the importance of flask positioning within the bath to obtain maximum cavitation within the flask.

US Probe

The ultrasonic bath above has a power output which is fixed (approx. 2 Wcm^{-2}), whereas the ultrasonic probe [Figure 1.3] has a power output which can be adjusted to suit the application up to a maximum of approx. 100 Wcm^{-2}. The probe can also be immersed directly into the solution, which provides a more efficient method of energy transfer. The probe is made of titanium (alloy 64) with a replaceable tip, which is essential since the tip becomes eroded with constant exposure to cavitation. The acoustic frequency can be varied for optimal performance although most equipment has a fixed frequency of 20kHz.

Figure 1.3 Ultrasonic Probe with Suslick Cell[3]

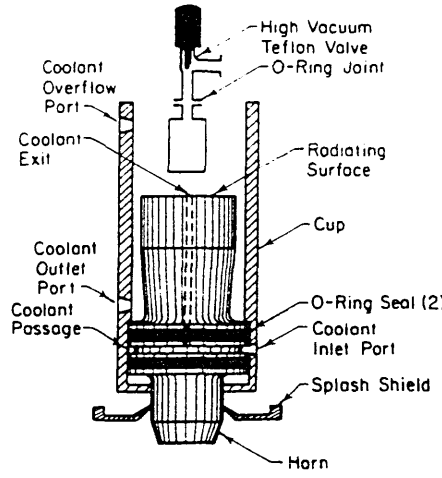


The sample size can be varied significantly and microtips may be used to introduce ultrasound into small quantities (2ml) of solution. The main disadvantages are temperature control of solution and the aforementioned erosion of the tip and consequent titanium contamination of the solution. A development of the US probe is the Suslick cell which allows high intensity sonication of a small sample (5-10ml) under nitrogen. It is pictured with the ultrasonic probe in Figure 1.3.

Cup-Horn Sonicator

This is a type of relatively high intensity US bath. The cup horn [Figure 1.4] is bolted directly onto a transducer that is normally affixed to the US probe. Water is circulated around the horn to act as a coolant and to provide a bath into which small flasks or vials can be immersed. The sample size is limited (50ml RB flask) but temperature control is not a problem and the sample is isolated in its own flask preventing any possible metal contamination.

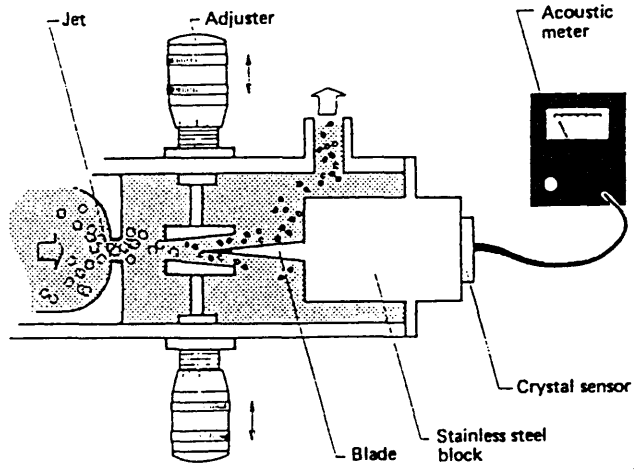
Figure 1.4 Cup-Horn Sonicator[3]



Industrial Whistle Reactor

The whistle reactor [Figure 1.5] is used in industry for mixing and emulsification purposes. Emulsification maybe required for promoting reactivity in heterogeneous systems, or it can simply be a physical requirement such as in the production of mayonnaise in the food industry. The effect is obtained by pumping the liquid at certain pressure and flow rates over a blade which then vibrates to produce ultrasound.

Figure 1.5 Whistle Reactor



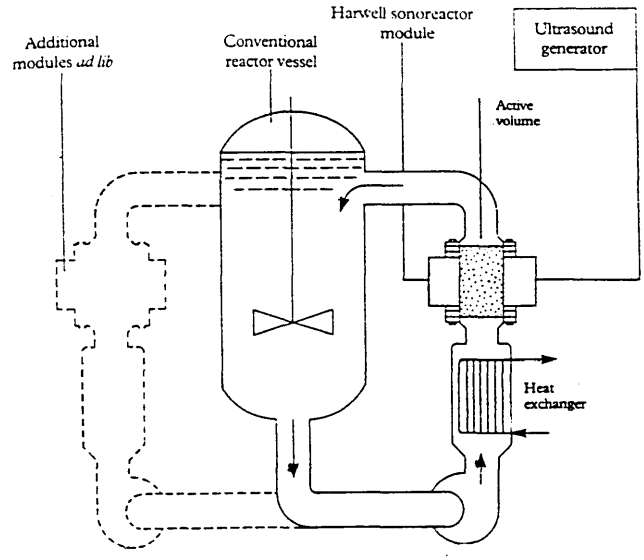
Adapted from R.S. Davidson,*et al., Ultrasonics*, **25**, 35, (1987).

Although this is an ideal flow system which is rugged and durable, the ultrasonic power is limited, and this equipment has not been used in sonochemistry.

Harwell Sonochemical Reactor

The research group at Harwell Laboratories[22] have designed a loop reactor for pilot plant scale sonochemistry [Figure 1.6]. This equipment sonicates a solution pumped from a holding tank through a reactor which is irradiated with high intensity ultrasound (1500W), and back to the holding tank. This effectively creates a reactive zone and a "quiet zone".

Figure 1.6 Harwell Loop Reactor[22]

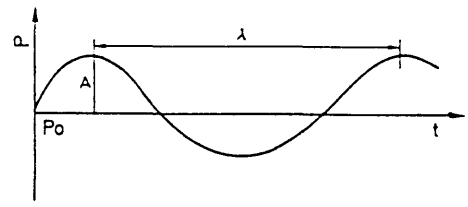


1.2 PHYSICAL ASPECTS

1.2.1 CAVITATION

The reason that ultrasound produces the chemical effects is attributed to the effect known as cavitation, which was mentioned earlier. Cavitation is formed when the liquid is subjected to ultrasound (acoustic) waves, which can be represented as a periodical variation of pressure P_m around a medium value P_o [Figure 1.7].

Figure 1.7 Sinusoidal Wave Propagation[2]

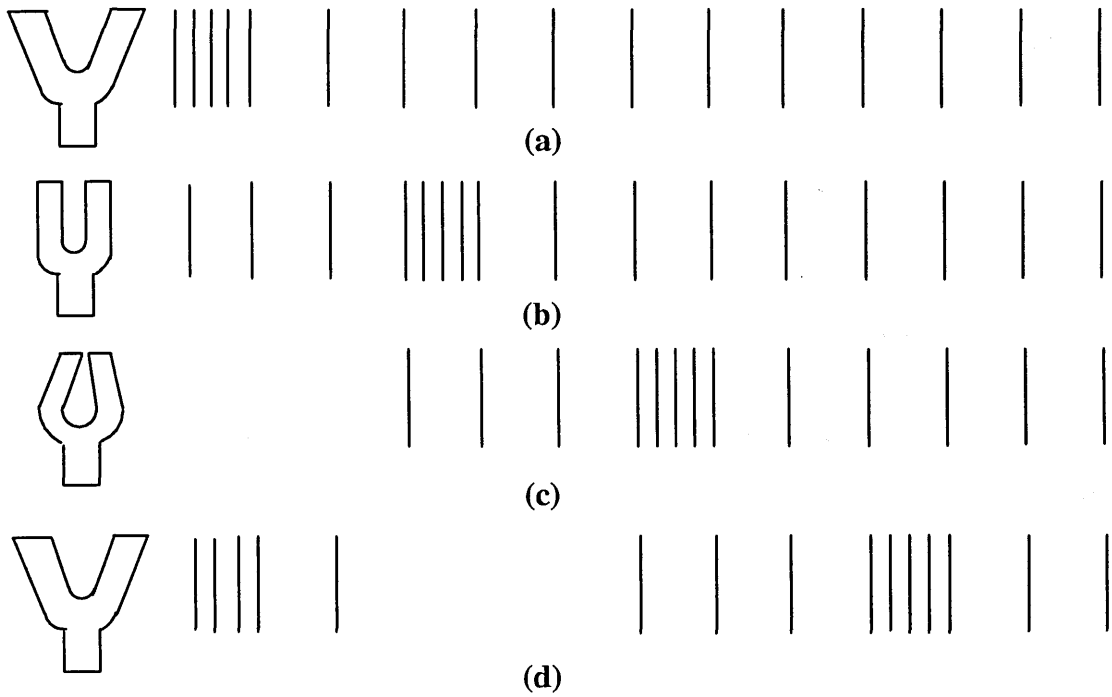


$P_m = P_o + A \sin \frac{2\Pi c}{\lambda} t$

c = sound velocity
λ = wavelength

If the amplitude of the acoustic wave is large enough, forces will develop which can break the cohesive nature of a liquid and cavities will form, i.e. intermolecular bonds, which give the liquid its volatility, viscosity, and surface properties will break to form a void or cavity during the negative half cycle of the wave. The following pressure cycle will cause this cavity to collapse violently. This movement of a transducer can be visualised diagrammatically [Figure 1.8] as the movement of a tuning fork in air which illustrates how compression and rarefaction waves are produced.

Figure 1.8 Pressure and Rarefaction Cycles[6]

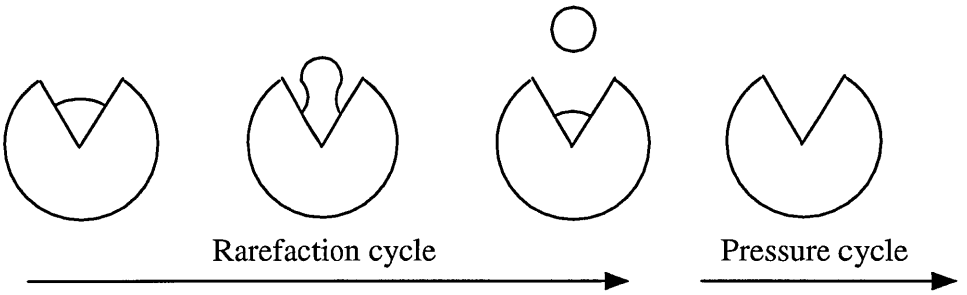


Pressure Waves in air

If we consider the right prong to be the transducer, then as it moves forward it compresses the layer of air next to it **(a)**. The fork returns to its original position, **(b)**, before moving to the left to leave a rarefaction region, **(c)**. On its second forward stroke to the right it begins another compression layer, **(d)**. Therefore any medium that is sonicated is subjected to compression and rarefaction cycles, creating microscopic bubbles which are violently imploded, causing the high local temperatures and pressures associated with cavitation.

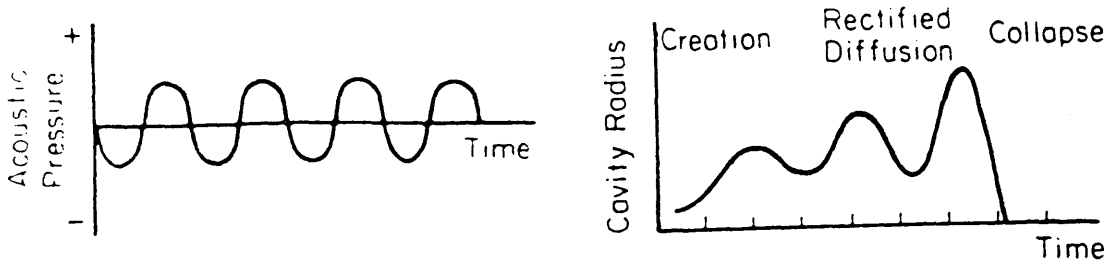
The nucleation of cavitation is assisted by any heterogeneous impurities (usually gas bubbles or solid particles present in the solution) that will disrupt the cohesion of the liquid; indeed, these contaminants are essential for cavitation to occur in a liquid [Figure 1.9]. Water for example has a tensile strength in excess of 1000 atmospheres[23] which would be impossible to break using ultrasonic intensities commonly available. The nucleation site proposed generally involves gas trapped in acute angle crevices of particulate contaminants[24-26] which lowers the tensile strength of the liquid. Nucleation occurs during the rarefaction cycle i.e. as the pressure decreases, and the liquid gas interface becomes increasingly convex until at a sufficiently low pressure it breaks away and produces a bubble.

Figure 1.9 Cavitation Nucleation



The resultant implosive collapse of bubbles creates microcavities[27] which then serve as further nucleation sites. Once initiated, cavitation falls into two general categories[28]: stable and transient. Transient cavitation is a short lived bubble that undergoes large changes in size within a few acoustic cycles then violently collapses causing the high temperatures and pressures attributed as causing chemical effects [Figure 1.10]. In stable cavitation a bubble oscillates many times with a limited change about its equilibrium radius. Both of these types of cavitation can occur simultaneously.

Figure 1.10 Bubble Growth[3]



The resonant size (R_r) of a transient cavity depends upon the frequency of ultrasound used. At 20kHz, a common frequency for laboratory equipment, R_r is calculated to be 170μm, whereas as the frequency is increased R_r decreases[3], at 1MHz R_r = 3.3μm. The voids produced by cavitation obviously vary in size and the sizes quoted above are close to the optimum to produce effective cavitation for sonochemical effects.

Hot Spot Theory

As stated earlier Lord Rayleigh predicted enormous temperatures and pressures resulting from cavitation. The mathematics of cavitation are complex and several reviews of acoustic cavitation dynamics have been published[29,30] however a review by Lorimer and Mason[6] provides approximate solutions to evaluate two important parameters, the maximal temperature (T_{max}) and pressure (P_{max}) reached at the end of the collapse cycle.

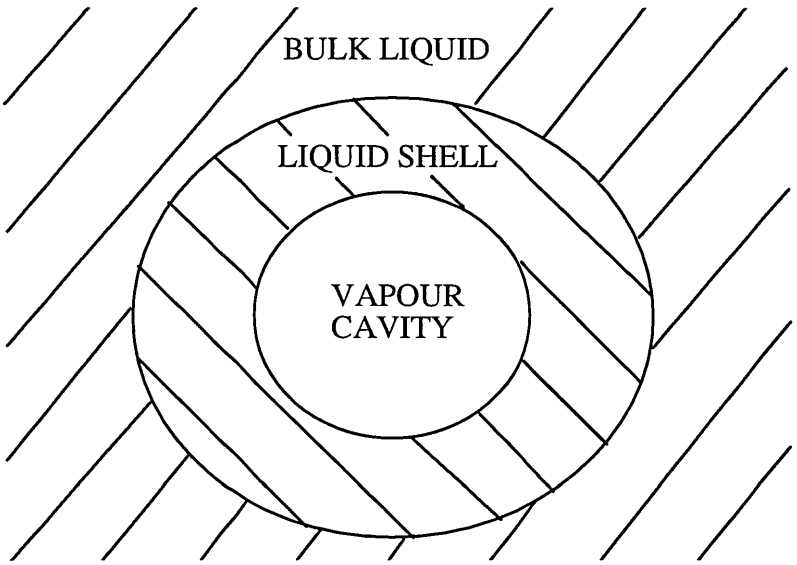
$$T_{max} = To \left[\frac{Pm\ (\gamma - 1)}{P} \right]$$

$$P_{max} = P \left[\frac{Pm\ (\gamma - 1)}{P} \right]$$

To is the macroscopic temperature, Pm is the pressure in the medium (the sum of the acoustic and hydrostatic pressures), P is the vapour pressure of the liquid and γ its polytropic ratio (Cp/Cv) of the constant pressure and constant volume specific heats.

Using these equations for a wave propagating in water, the theoretical maximum temperature (T_{max}) would be several thousand degrees K, and the maximum pressure (P_{max}) hundreds to thousands of bar. It is from these values that sonochemical effects are interpreted[31] from the so called "Hot Spot Theory". These predicted values are less than the original predictions made by Rayleigh of 10,000 K and 10,000 atm. However the temperatures and pressures are still large and sonochemical reactivity is believed to occur in the cavity or in its immediate vicinity in the liquid shell surrounding the cavity[32] [Figure 1.11].

Figure 1.11 Liquid Shell[3]



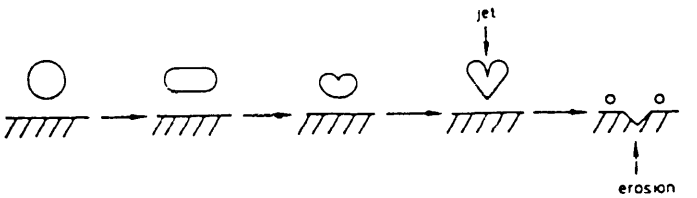
Empirical evidence for the hot spot theory relies on several studies which have involved spectral analysis of sonoluminescent emission[33-35] and also comparative rate "chemical thermometry" in which[36,37] relative rates of CO dissociation of metal carbonyls were determined as a function of substrate vapour pressure and then analysed using activation parameters determined previously by gas-phase laser pyrolysis. This study also estimated the volume ratio of gas to liquid zone [Figure 1.11] to be approximately 10^5. A kinetic and mechanistic study of the sonochemical reactions of *p*-nitrophenol in oxygenated aqueous solutions has estimated the average effective temperature of the interfacial region surrounding the cavitation bubbles to be approximately equal[38] to 800 K. These studies have shown that high temperature hot-spots are produced and it is currently accepted that the existence of the very high temperatures can produce the effects such as radical production and sonoluminescence, and the release of the pressure as a shock wave can account for increased chemical reactivity due to increased molecular collisions.

Heterogeneous Systems

Liquid-Solid

When heterogeneous liquid-solid systems are subjected to ultrasound the nature of collapse of the cavitation bubble changes dramatically. Instead of the symmetric collapse, an asymmetric collapse occurs which generates a jet of liquid directed at the solid surface. There is microphotographic evidence of this taken by Ellis[39,40] and Lauterborn[41], who have measured jet velocities greater than 100 ms^{-1}. The asymmetric collapse of a bubble begins with slight elliptical asymmetry which is self-reinforcing and terminates in a jet which can deform the solid surface [Figure 1.12].

Figure 1.12 Microjet Formation[2]



The impingement of this jet on the surface can have two effects. The impact can remove a small particle, which due to its size, is of high reactivity, and the sonic wave then efficiently mixes the two phases into a pseudo liquid-liquid system. Solids of low cohesion energy such as sodium are easily dispersed[42] using ultrasound. Secondly, if the impact is unable to disperse the solid, it constantly cleans the surface, by removing passivated layers and providing mass transport of reactants. This can lead to an increase in reactivity or an alteration in the reaction pathway and selectivity which will be discussed later (Section 1.3.3).

Acoustic streaming (or microstreaming) is an effect which also should be mentioned here. This phenomenon is independent of cavitation. Here the liquid absorbs energy from the propagating acoustic wave, and due to the conservation of momentum the liquid must also gain momentum. This creates force gradients and mass transport, therefore when the liquid-solid boundary is subjected to ultrasound, improved mass transport occurs suppressing diffusion layers which are common limiting factors[43,44] for such reactions.

Liquid - Liquid

The main effect of ultrasound on heterogeneous liquid-liquid systems is emulsification, which is used widely[7] in industry. The physical effects of emulsification are greatly increased surface area of contact between the two immiscible liquids, therefore ultrasound can be expected to have an effect similar to phase transfer catalysis. Homogeneous sonochemistry will be discussed fully in Section 1.3.1.

FACTORS AFFECTING CAVITATION

Given the number of variables that can be altered within the experiment, it is worthwhile discussing how these parameters can effect cavitation throughout its cycle, i.e. nucleation, bubble growth and collapse.

a) Frequency

As the frequency of ultrasound is increased, production of cavitation[45,46] decreases. This can be explained[47] by the finite time required for a bubble to form to a sufficient size to cause any disruption. As the frequency is increased, the rarefaction cycle time is reduced which reduces the time available for a void to form. It also follows that if a cavity does form, the time taken for it to collapse is longer than the compression cycle of the acoustic frequency. The higher rates of molecular motion provided by the higher frequencies also result in greater power losses. At 400 kHz ten times more power is required to make water cavitate than at 10 kHz. Therefore, 20-50 kHz has been the frequency range utilised for cleaning equipment, and its subsequent application to sonochemistry.

b) Solvent

The rarefaction cycle has to overcome the cohesive force of the solvent to form a void or cavity, therefore cavitation should be more difficult in viscous liquids, and indeed such an effect does occur[48]. Low viscosity solvents such as carbon tetrachloride do require less sound pressure to produce cavitation. However, this has to be balanced with the fact that solvents with higher vapour pressure (P) undergo less cavitational effects. This is demonstrated from the calculated T_{max} equation stated earlier. The T_{max} and P_{max} will decrease as P increases. This is easily explained using the "hot spot theory". As P increases the cavity will be more readily filled with solvent vapour. This will in effect cushion the collapse of the cavity and reduce P_{max} & T_{max}.

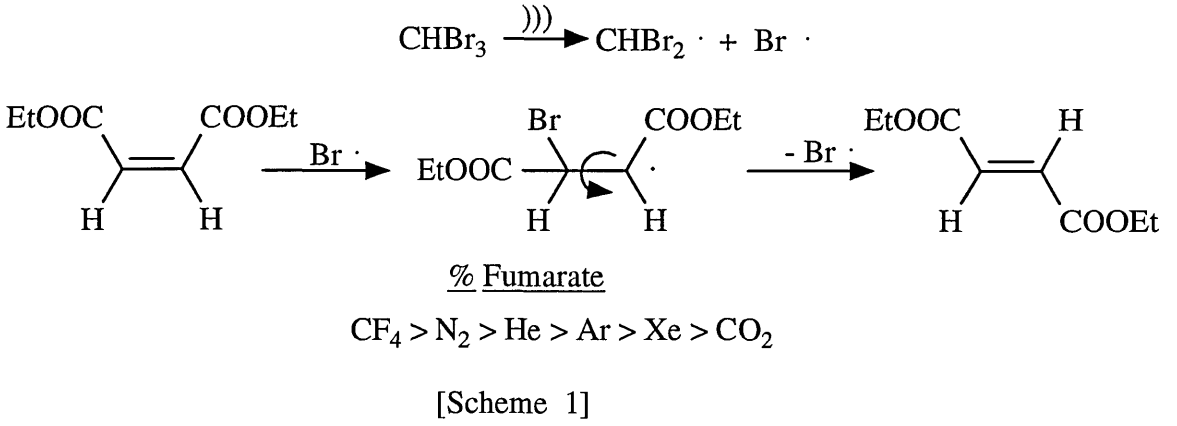
c) Temperature

As temperature is increased, P will increase and so lower T_{max} & P_{max} for the reasons explained above. This would suggest that lower temperature favours effective cavitation. However, it was observed by Rosenburg[49] that, in several liquids, the amount of aluminium eroded in a 8 kHz ultrasonic field did in fact increase from -10 °C to 50 °C then decreased from 50 °C to 90 °C. The initial increase arises from increased nuclei for cavitation provided by gas coming out of solution, then the subsequent decrease in erosion with increase in temperature as the internal vapour pressure (P) increases with the resultant damping of the shock wave as the cavity implodes. In general however sonochemical reaction rates slow with increased temperature.

d) Gas Type and Content

Using the previous equation, gases with large polytropic ratios will provide greater sonochemical effects. These are monoatomic gases (He, Ar, Ne) rather than diatomics (N_2, O_2). This is a simplistic view and thermal conductivity of the gas has to be considered as well as gas solubility. Liquids with a higher concentration of dissolved gas will have a lower cavitation threshold (increased nuclei). However, this dissolved gas will cushion the cavitation implosion and reduce effectiveness, and there is a direct correlation[50] between gas solubility and cavitational intensity. The removal of gas completely will reduce available nuclei and cavitation will become increasingly difficult. Also irradiating a solution with ultrasound has a degassing effect, thus consistency is affected. Therefore, workers either bubble gas through the system throughout the experiment (favoured) or pre-sonicate the system to degas it for a minimum of ten minutes before the experiment begins.

The role of the polytropic ratio (γ) has been questioned in a study where the inert perfluorocarbon gases CF_4 and C_2F_6 have been compared with nitrogen, argon, xenon, and carbon dioxide[51,52] in the isomerisation of diethyl maleate into diethyl fumarate in the presence of $CHBr_3$ *via* a radical intermediate [Scheme 1]. The highest percentage fumarate versus time was obtained from CF_4 which has a smaller polytropic ratio than xenon and CO_2 and similar polytropic ratio to argon. On the basis of these results the authors question the role of the polytropic ratio and the hot spot theory. They believe the results they obtained can be explained more readily from electrical theories since they state CF_4 is known to be an efficient gas in plasma chemistry.



[Scheme 1]

e) External (Applied) Pressure

Increased external pressure increases both the cavitational threshold and the intensity of cavity collapse. The increased external pressure will act as an antagonist to the effect of the rarefaction cycle, therefore the intensity of the ultrasound will have to increase to produce cavitation. However, if cavities do form the increased external pressure will cause the resultant collapse to be quicker and more violent. Therefore, higher external pressure allows cavitation to occur at higher frequencies than would normally be possible (see frequency effect).

f) Intensity

Intensity has a significant effect on reaction rates in sonochemistry. Below a threshold level the amplitude of sound is too small to promote nucleation. Above this threshold, as intensity is increased, the effective sonicated zone will increase and rate will increase. However, past a certain point, rate begins to decrease as intensity increases. There are two reasons for this: firstly, the cavity at the radiating surface is so intense the bubbles shroud the propagating sound waves; Secondly, the bubble grows so large (R_{max}) on rarefaction, that the time available for collapse is insufficient[53].

Relaxation Phenomena and Kinetics

Studies into relaxation phenomena from sinusoidal sound waves[54] have produced outstanding results in the field of binary mixtures, polymers and determination of thermodynamic mixtures. However these are outwith the scope of this introduction as is any explanation of kinetic studies such as reactions within the cavitation bubble, gas liquid interface, or on bubble collapse.

1.2.2 SONOLUMINESCENCE

Sonoluminescence is a phenomenon wherein light is emitted from a solution which is cavitating. It has been observed from almost the outset of cavitation studies by the use of the naked eye[55], exposure of photographic plates[56], photomultipliers[57] and image intensification[58] techniques. The arguements to explain why sonoluminescence occurs divide into two categories thermal and electrical.

Thermal theories

These rely on various explanations including the hot-spot theory of cavitation where the high temperatures produce incandescence. One variation of the hot-spot theory is the thermochemical theory where the high temperatures in the collapsing bubble dissociate or ionise molecules, and the resultant recombination of radicals[34,59,60] or ions[61] produce light. Jarman[62] proposed a mechanico-thermal theory where the cavitation collapse produces high pressures, temperatures, and light radiation similar to converging shock waves.

Electrical theories

These have been reported by several researchers who suggest[63,64] that charges form on opposite sides of a lens-shaped cavity, resulting in micro discharges which produce light. Margulis [65,66] disagrees with these theories and proposes his own, which are upheld by others[3,6] as more acceptable than the earlier theories. However, thermal theories are still considered to be the more acceptable explanation. There is spectral evidence[34] to show that sonoluminescence originates mainly from the recombination of radicals mentioned earlier.

1.3 SYNTHETIC APPLICATIONS

1.3.1 HOMOGENEOUS REACTIONS

Effect on Solvents

Aqueous

The effect of irradiating solutions with ultrasound has been examined since the beginning[12] of ultrasonic experiments. Cavitation is known to induce the homolytic cleavage of water[67,68] to produce hydrogen atoms and hydroxyl radicals.

$$H_2O \xrightarrow{)))} H\cdot + HO\cdot$$

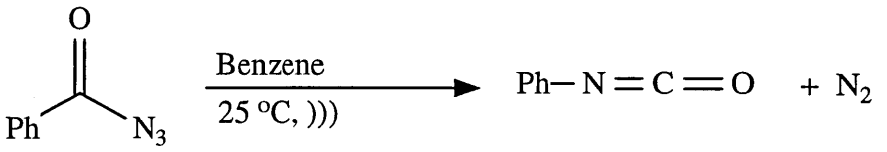
These highly reactive radicals can combine to produce hydrogen or hydrogen peroxide, or can react with solute molecules. Parke and Taylor[69] have shown the presence of hydroxyl radicals by producing *o-, m-, & p*-hydroxybenzoic acids by sonicating aqueous solutions of benzoic acids. The sonolysis and radiolysis of water to produce hydroxyl radicals and hydrogen atoms has also been shown[70] to degrade L-ascorbic acid. Other studies have shown that various products can be obtained by altering the type of gas dissolved[71] in the aqueous system. Ammonia[72], formaldehyde[73], and HCN[74] have all been produced by ultrasonic irradiation of solutions containing the gases i.e. nitrogen, carbon monoxide, hydrogen, and methane respectively.

Non-Aqueous (Organic Solvents)

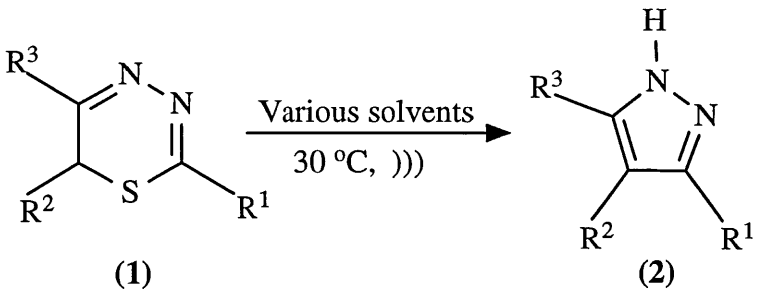
Most organic solvents have been shown to decompose to some degree under sonication, and the formation of free radicals has been shown[75] to occur readily using spin trapping and EPR studies. Polymers[76] and acetylene[77] are produced from aromatics, and hydrocarbons such as decane are cleaved[78] into various compounds. More volatile solvents are less affected, since these solvents cushion the cavitation with their inherent higher vapour pressure.

Organic Reactions

There are few monomolecular reactions which involve volatile molecules which have migrated into a cavity. An early example of such a reaction is the Curtius rearrangement of benzoyl azide to phenyl isocyanate when sonicated[19] in a benzene solution. The reaction proceeds at a higher rate than the stirred equivalent, however the yield is low (5%).

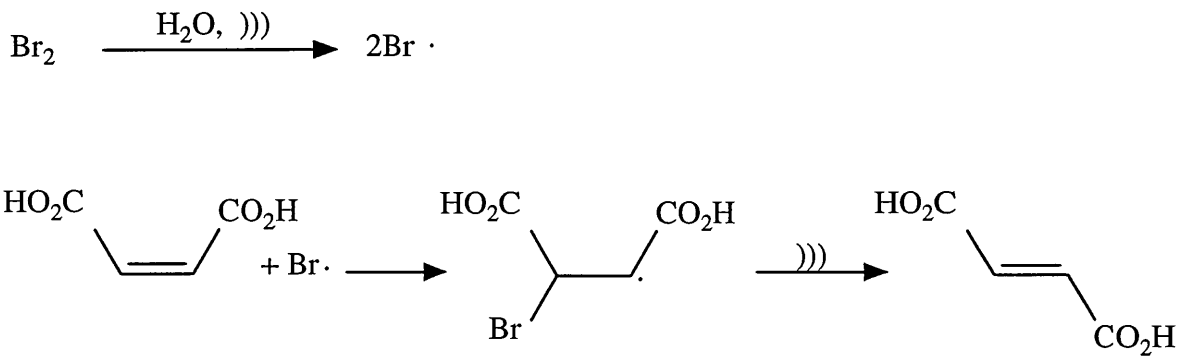


An efficient method of sulphur extrusion from 1,3,4-thiodiazines (**1**) to the imidazole (**2**) in high yield has been described[79]. This was carried out using high vapour pressure solvents in an ultrasonic cleaning bath.



(**1**) (**2**)

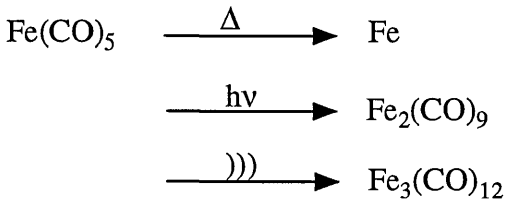
Isomerisation of maleic acid to fumaric acid in the presence of bromine or alkyl bromides was studied[80] by Elpiner. The reaction is initiated by the sonolysis of the bromine molecule to the corresponding radical [Scheme 2].



[Scheme 2]

Organometallics

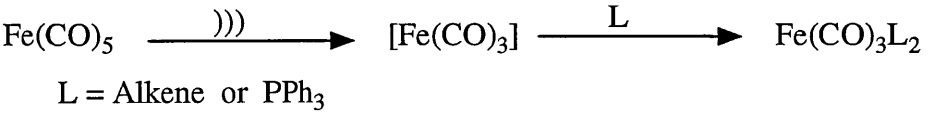
This area of monomolecular organometallic sonochemistry is dominated by the work of Suslick and co-workers. When compared to the photo- and thermolytic reactions of the same compound it was reported[81] that a unique product was formed when iron pentacarbonyl was sonolysed.



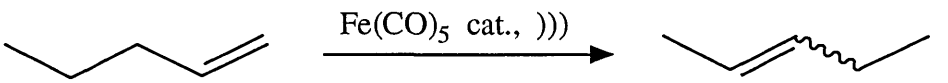
Solvent is shown to play an important role in the reaction. As solvent vapor pressure increases the selectivity also increases. This would indicate a relationship between selectivity and cavitation intensity, since the cavitation is less intense with increased vapour pressure.

Solvent	$Fe_3(CO)_{12}$ Yield (%)
Heptane	82
Octane	7
Decalin	4

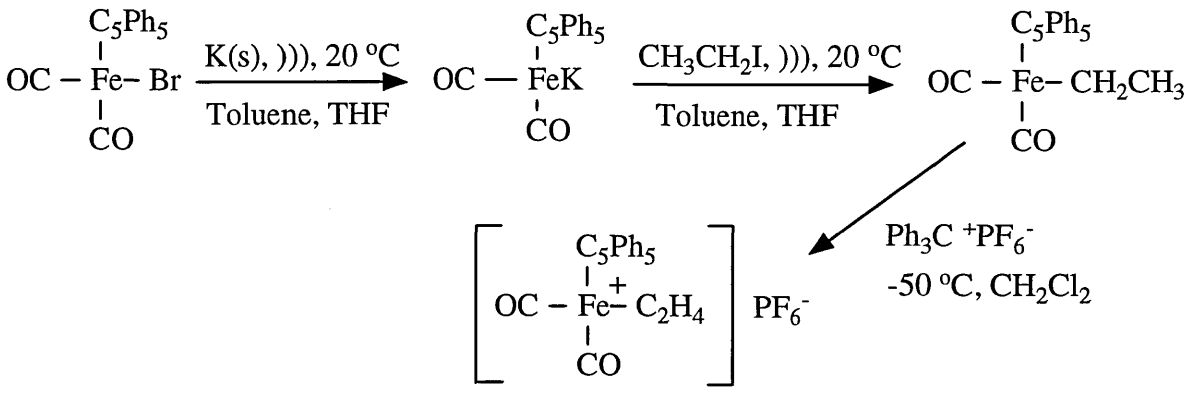
This work also illustrates how the intermediate species, iron tricarbonyl, can bind to an added Lewis base such as phosphine or alkene added to the mixture.



When an alkene is used, isomerisation occurs at a rate 10^5 higher than the equivalent silent reaction.



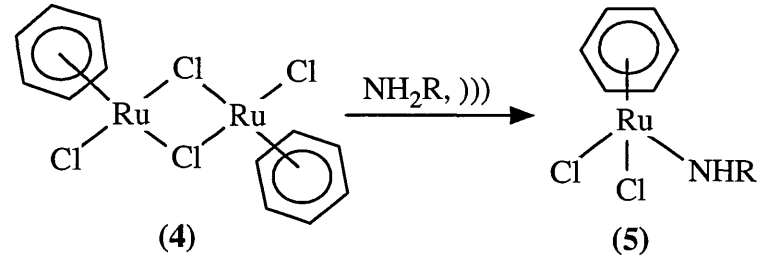
Other synthetic complexes of Fe have been prepared[82] such as the novel cationic Fe (II) complexes that contain a pentaphenylated cyclopentadienyl ligand (C_5Ph_5), e.g. $[Fe(C_5Ph_5)(CO)_2(C_2H_4)]PF_6$ **(3)**. Previous synthesis of this type have been difficult under conventional methods since neutral or cationic complexes are sparingly soluble in common organic solvents. Ultrasound, therefore, helps stabilise such compounds in this type of synthesis. Ultrasound is also used to create a fine dispersion of potassium in the first step of the preparation [Scheme 3].



(3)

[Scheme 3]

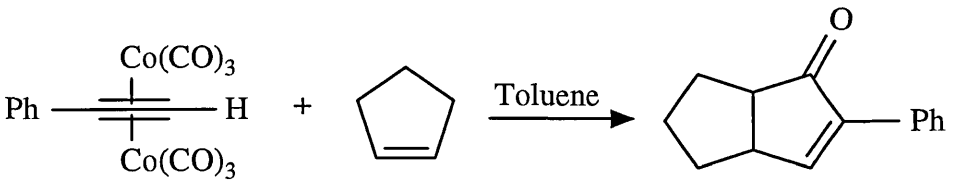
Ultrasound is also used to increases the solubility of bridged organometallic compounds such as the $[(arene)Ru_2Cl_2]_2$ complex **(4)** which can be reacted[83,84] with nitrogen - donor ligands.



(4) **(5)**

R = Et, C_6H_4Me, CMe_3

Other sonochemical organometallic reactions which have been published include a Pausson-Khand annulation[85,86], a modification of this involving chiral ligands[87], and also an alkynone hydration[88] reaction [Scheme 4].



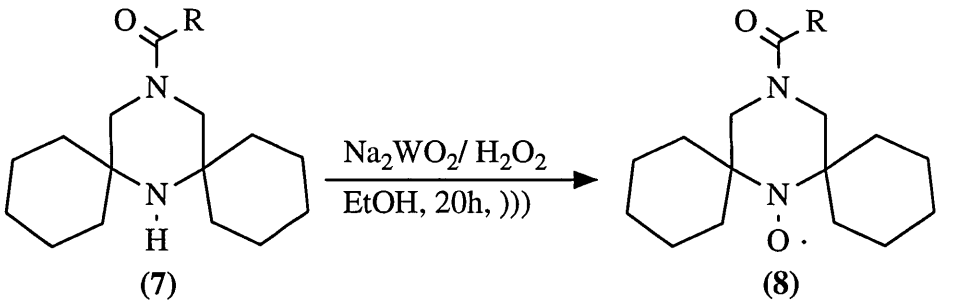
(6)

Conditions	Yield
Stir, 110°C, 36hrs	42%
))), 3hrs	49%

[Scheme 4]

Oxidation

As stated earlier cavitation can provide the highly reactive hydroxyl radical which in theory can be utilised as an oxidising agent. However, ultrasound does not provide these radicals in high enough concentrations to be of synthetic value. Ultrasound can be used to "excite" oxidising agents such as hydrogen peroxide, as seen in the oxidation[89] of hindered piperazines (**7**) to nitroxyl radicals (**8**) [Scheme 5]. Practically no reaction occurs with stirring only.



(**7**) (**8**)

R	Yield (%)
$(CH_2)_4CH_3$	63
$(CH_2)_{16}CH_3$	86
$C_6H_4O(CH_2)_7CH_3$	58

[Scheme 5]

Solvolysis

The solvolysis of t-butyl chloride in aqueous ethanol[90] to the corresponding ether was accelerated by a factor of 20 using ultrasound. It was found higher reaction rates occurred at lower temperatures (10 °C), and at the solvent composition of 60 wt% ethanol [Figure 1.13]. A correlation is found between the rate enhancement and the sound absorption composition curve of the solution. The authors propose a three dimensional structural rigidity within the solvent which the alcohol enhances up to a maximum point causing the solution to absorb more sound energy, which in turn raises the ground-state energy of the t-butyl chloride increasing the solvolysis rate.

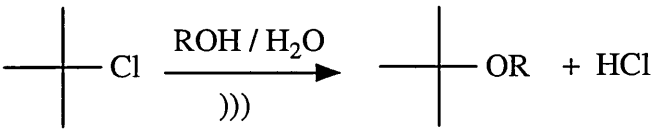
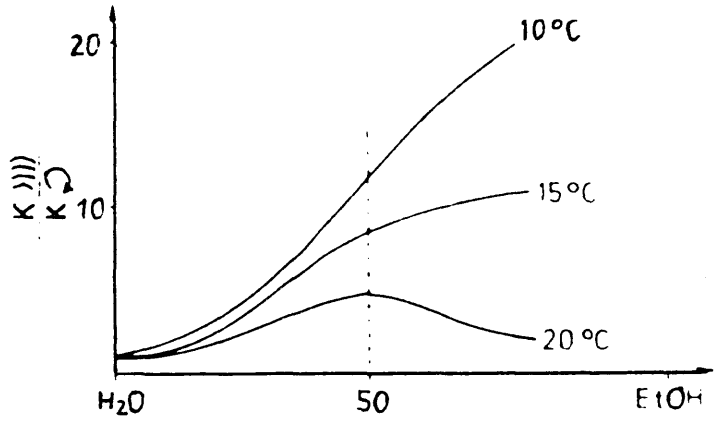
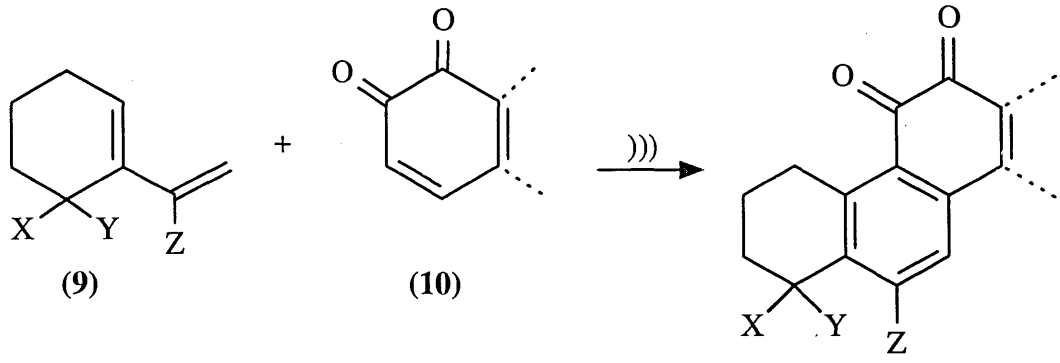


Figure 1.13 Sonolysis of t-Butyl Chloride[90]



Additions

The Diels-Alder reaction was targeted as a potential synthetic application for ultrasound since heat and pressure can be used to promote the cycloaddition. Initial work had little success[91,92] but Snyder *et al.*[93-97] has reported that an electron rich diene **(9)** will add to various ortho-quinones **(10)** to yield the product **(11)**.



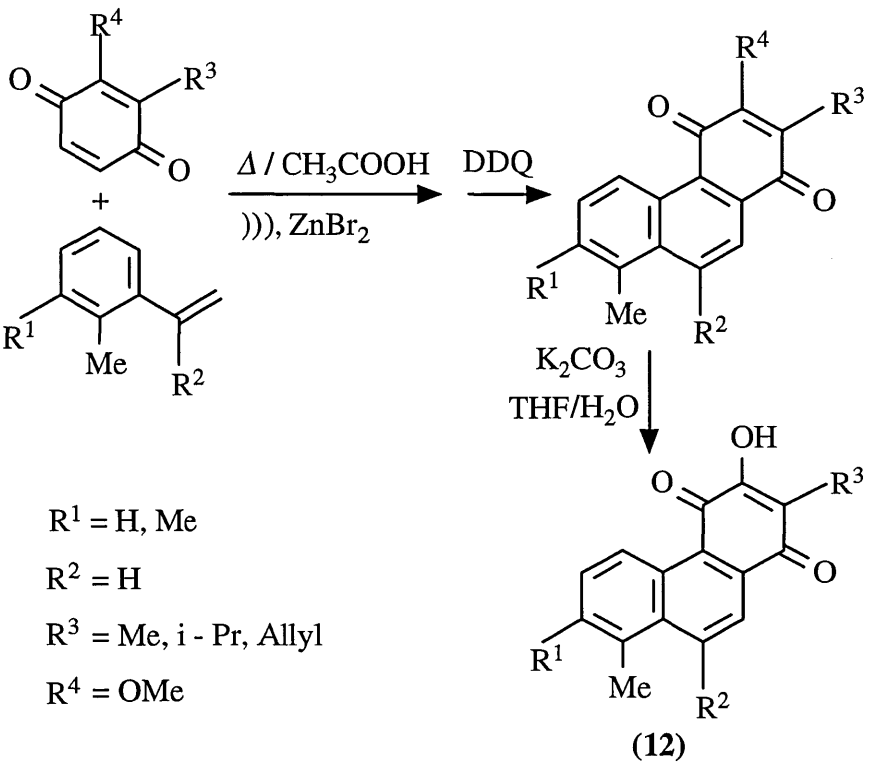
(9) **(10)**

X,Y,Z = H or oxygenated groups **(11)**

The authors report improved yields, regioselectivity, and reactions with no solvent required. This enhanced reactivity can be interpreted using the "hot spot theory" where the high temperatures and pressures encountered in cavitation can enable these reactions to take place without the use of external pressure.

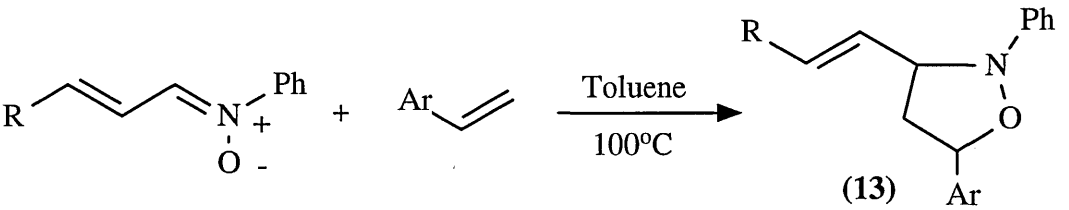
A series of substituted phenanthrene-1,4-quinones **(12)** were synthesised[98] by ultrasound - promoted and Lewis acid catalysed, highly regioselective cycloadditions of styrenes with substituted 1,4-benzoquinones. Compared to thermal reactions the

sonochemical cycloadditions have improved yields and high regioselectivities, which resulted in pure plectranthon D (R^1& R^2=Me, R^3= Allyl, R^4=OMe) being prepared for the first time [Scheme 6].



[Scheme 6]

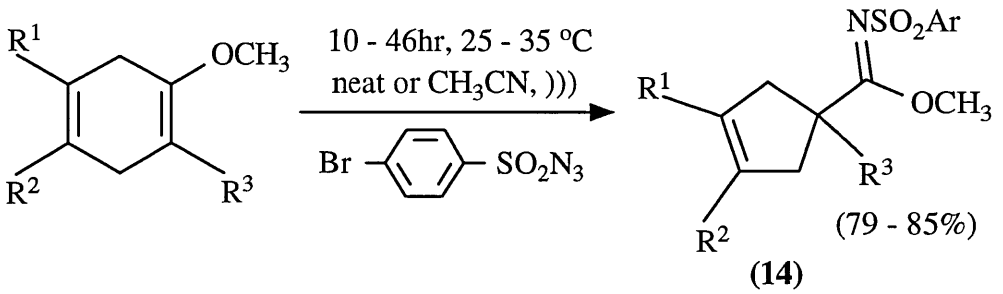
Under the influence of ultrasound nitrones add to olefins[99] in 1,3-dipolar cycloadditions to afford the product **(13)** a far shorter time compared to the silent reaction although the yields are not improved [Scheme 7].



Ar	Conditions	Time/h	Yield (%)
Ph	Stir	34	80
Ph	)))	1	81
4-ClC_6H_4	Stir	24	75
4-ClC_6H_4	)))	1	75

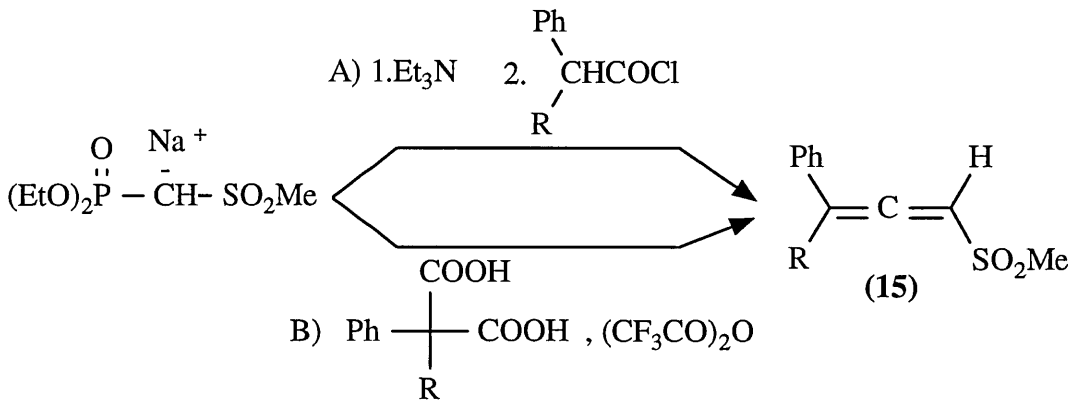
[Scheme 7]

Methyl cyclohexenyl ethers[100] undergo cycloaddition-rearrangement reaction to the product **(14)** with p-bromobenzenesulfonyl azide. The overall yield is not improved with ultrasound but the reaction rate is increased, and the reaction can be carried out at atmospheric pressure, compared with previous usual conditions of 10 kbar. Ultrasound also allows reactions to be carried out on a larger scale (4 mM, cf. 0.25 mM). This reaction can be compared to the rate acceleration observed in the Diels-Alder cycloaddition. Both of these reactions normally require high pressure to obtain high yields; ultrasound provides an alternative route at atmospheric pressure on the macro scale. The rate acceleration can be attributed to cavitation with the resultant high pressures and temperatures on the micro scale.



(14)

Ultrasound has been used[101] to improve the yield in the preparation of allenyl sulfones **(15)** from condensation of sulfonylmethylphosphate anion with acid chlorides in the presence of triethylamine, or, alternatively the anions react with arylalkylmalonic acids in the presence of trifluoroacetic anhydride [Scheme 8]. The sonochemical method has a more marked effect on method B, probably due to the low vapour pressure solvent DME increasing the cavitational intensity.

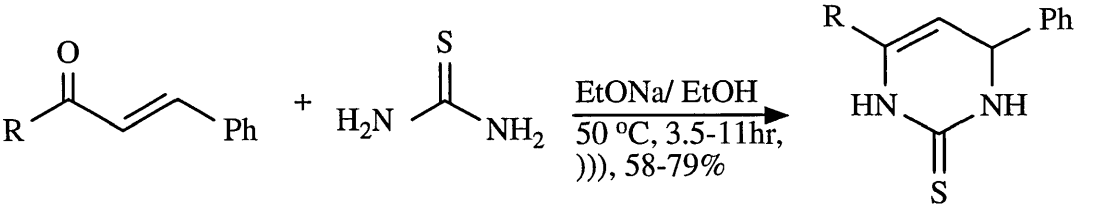


(15)

R	Method	Solvent	Yield (%) Stir	)))
CH_3	A	DCM	10	15
	B	DME	19	63
C_2H_5	A	DCM	25	30
	B	DME	16	77
C_6H_5	A	DCM	35	41

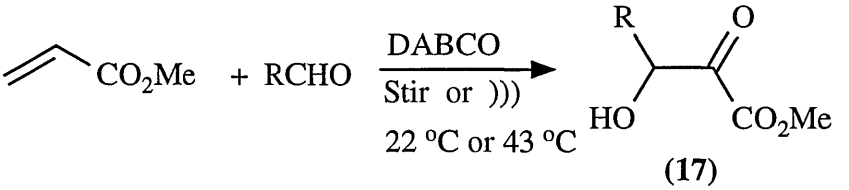
[Scheme 8]

Sonication also improves the selectivity of base catalysed additions of thiourea with ferrocenyl chalcones to form the cyclic compound **(16)**. The thermal equivalent[102] of this reaction produces inseparable mixtures.



(16)

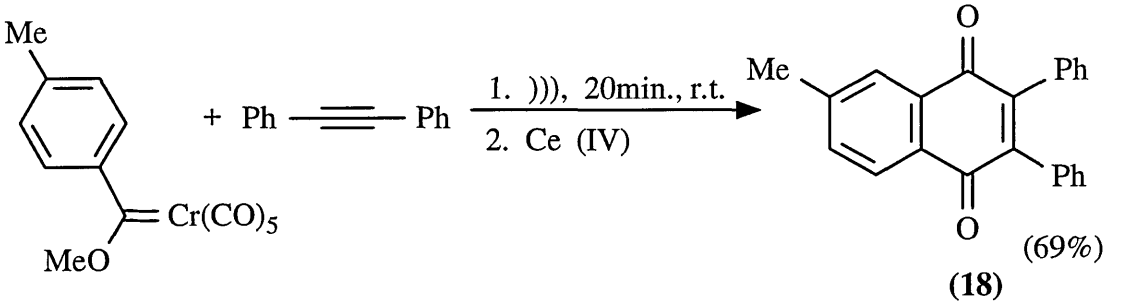
Slight to moderate rate enhancements have been reported[103] with the sonication of Bayliss-Hillman reactions. In this reaction aldehydes are coupled with methyl acrylate using DABCO (1,4-diazabicyclo[2.2.2]octane) as a catalyst to produce the compound **(17)**. The authors report that pressure on a macro scale had been used and have therefore reasoned that ultrasound was a practical alternative to apply pressure on a micro scale. Yields are not quoted but reaction rates are stated as being increased by 4 - 43% on reactions that were carried out over a time period as long as ten days. The authors also mention[104] sonicating a reaction which took 2-3 months to complete!



(17)

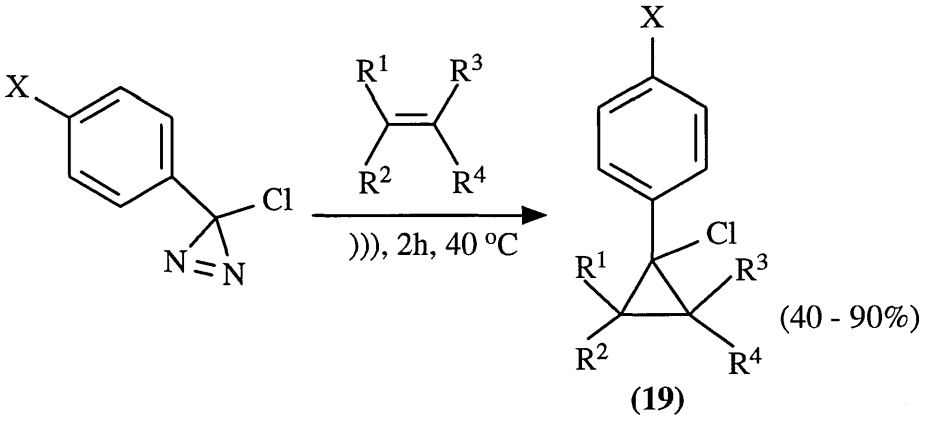
R = Me, Et, i-Pr, Ph, C_6H_{11}))), 4 - 43% rate increase

Using a variety of substrates, sonication[105] was found to promote the chromium carbene Dotz annulation at room temperature. Sonication of a solution of the metal carbene complex and alkyne in di-*n*-butyl ether rapidly produced the six-membered ring product **(18)** in moderate to good yield. These results coincide with the findings of other groups on the benefits of ultrasound[2,3] in organometallic chemistry.



(18)

The synthesis of a variety of cyclopropanes has also benefitted from ultrasonically induced decomposition of diazirines to produce carbenes[106] which are then trapped by olefin substrates as cyclopropanes **(19)** [Scheme 9]. The yields were compared favourably to yields obtained in photolysis.



(19)

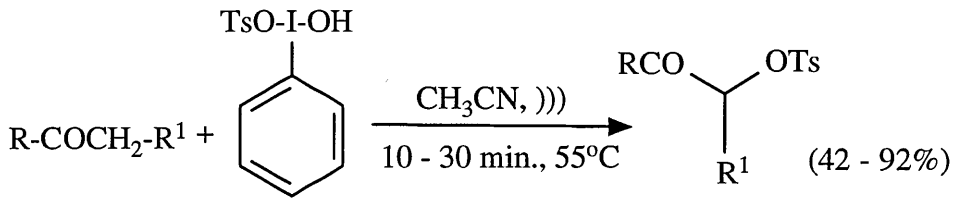
X = H, Cl, Me R^1 = H, CO_2Et, Me, Cl R^2 = H, Me, Cl

R^3 = H, Me R^4 = CH_2Br, CO_2Et, Cl

[Scheme 9]

Ultrasound allows the α-tosylation of ketones with [hydroxy(tosyloxy)iodo]benzene under mild conditions[107] in a short period of time. Thus, ketones are reacted in acetonitrile with the tosylating agent to give good yields of α-tosylates **(20)**.

The method allows the dispersion of this reagent which is usually insoluble in acetonitrile at these temperatures, and avoids the time consuming preparation of intermediates such as trimethylsilyl enol ether derivatives and α-hydroxyketones [Scheme 10].



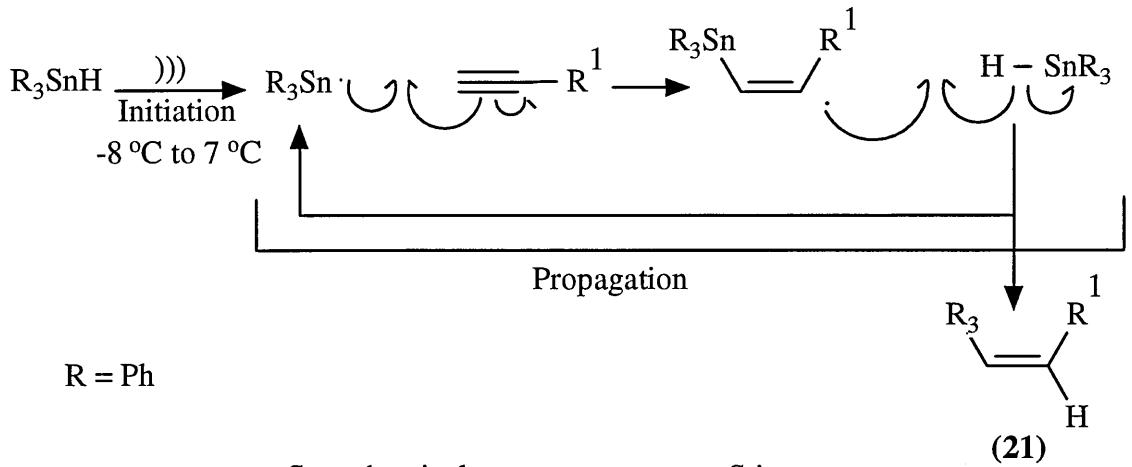
R = Me, Et, Ph

R^1 = H, Et, Ac

(20)

[Scheme 10]

Homogeneous sonochemistry has been used to good effect for the controlled initiation of radical hydrostannation[108] of alkynes to vinyl compounds **(21)**. The sonochemically initiated reaction compares well with the thermally initiated reaction and rate acceleration is impressive. It is believed that selective thermolysis of the tin hydride reagent in the region of the short-lived hot spots leads to the high kinetic cis selectivity of the sonochemical method. It can be clearly seen that yields and reaction rate are improved significantly under sonochemical conditions [Scheme 11].



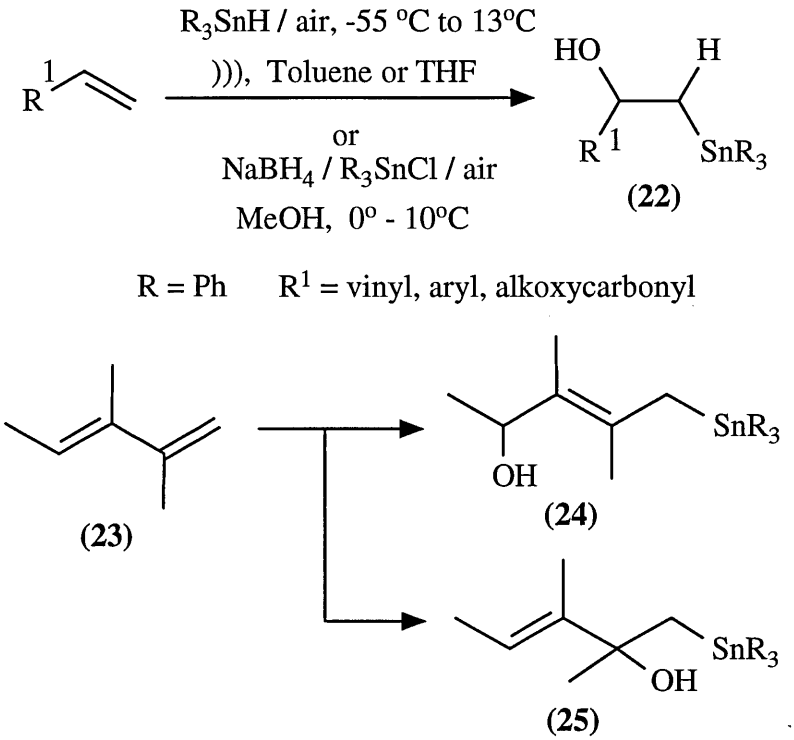
R = Ph

(21)

		Sonochemical			Stir	
R^3	Solvent	Time/	Yield	(% cis)	%Yield	Acceleration
n-Bu	neat	3	95	(92)	1	>1 x 10^2
n-Bu	toluene	2	86	(91)	3	1 x 10^2
Ph	toluene	4	50	(≥92)	13	circa 10
Me_3Si	toluene	5	78	(8)	0	>6 x 10^2

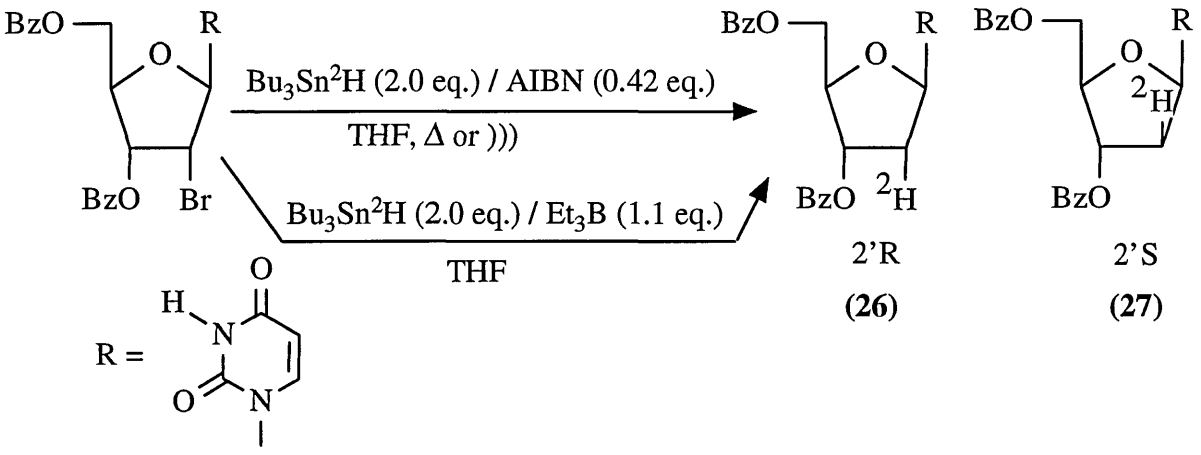
[Scheme 11]

The hydrostannation of alkenes and alkynes to vinyl compounds by the method outlined above can be modified[109] by the presence of air. Addition of stannyl and hydroxyl groups across the C-C multiple bond occurs resulting in a hydroxystannation reaction producing hydroxy stannane (**22**). The reaction can also proceed using dienes (**23**) to produce β-hydroxy stannanes (**24**) or hydroxylated allylic stannanes (**25**) [Scheme 12]. The reaction was found to proceed *via* a radical mechanism. Ultrasound was found to initiate the radical reaction efficiently compared to stirring only. But it was found that chemical (AIBN) and photolysis of the reaction mixture initiated the reaction just as efficiently. The tin hydride reagent was also replaced using a mixture of tin(IV)chloride and $NaBH_4$ which produced an in situ source of tin hydride.



[Scheme 12]

Sonochemical Bu_3Sn^2H reduction of a 2'-bromo-2'-deoxyuridine benzoate at -71°C results in highly efficient deuterium incorporation[110] to afford a 96:4 ratio of (2R')-(**26**) vs (2'S)-(2'-^{2}H)-2'-deoxyuridine (**27**). The equivalent AIBN/thermolysis method at that temperature did not proceed but use of Et_3B as an alternative radical initiator allowed a high yield at low temperature [Scheme 13].



Method	Temp (°C)	Time (min.)	% yield	2'R / 2'S
AIBN / thermolysis	65	60	93	82 / 18
"	0	60	trace	
AIBN /)))	-72	360	78	96 / 4
Et_3B	-52	90	90	92 / 8

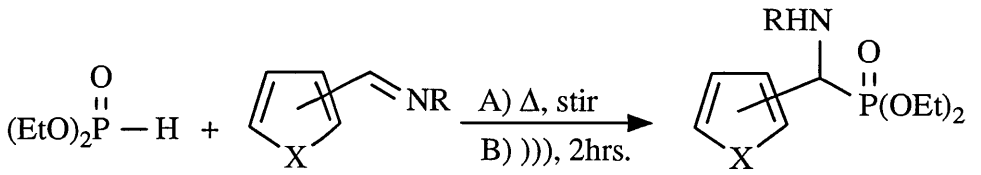
[Scheme 13]

It was found that the halo compounds *p*-iodoanisole and 1-halonaphthalenes (Cl, Br, I) could be reacted with $Ph_2P\cdot$ radicals to produce the phosphine **(28)**[111,112] in liquid ammonia at room temperature and pressure (9kg/cm^2) when the reaction mixture was sonicated. This reaction proceeds *via* a $S_{RN}1$ mechanism and normally requires cooling to -33 °C under quiet conditions. It was found that ultrasound increases reaction rate and yield which agrees with other work[2] on $S_{RN}1$ reactions.

$$RX + Ph_2P\cdot \xrightarrow[\text{r.t., 15 - 60 min.}]{NH_3\ (l),\ )))} \underset{\textbf{(28)}}{RPPh_2} + X^- \qquad (20 - 94\%)$$

RX = *p*-iodoanisole, 1-iodo-, 1-chloro-, or 1-bromonaphthalene..

The synthesis of α-aminophosphonic acids *via* aminophosphonic esters from diethyl or dibenzylphosphonates and substituted imines was found[113] to be improved with sonochemical activation. Ultrasound was applied to the preparation of the phosphonates in this synthesis. The main advantage was the reduction in the lengthy time period required for this reaction (480 hrs) [Scheme 14].



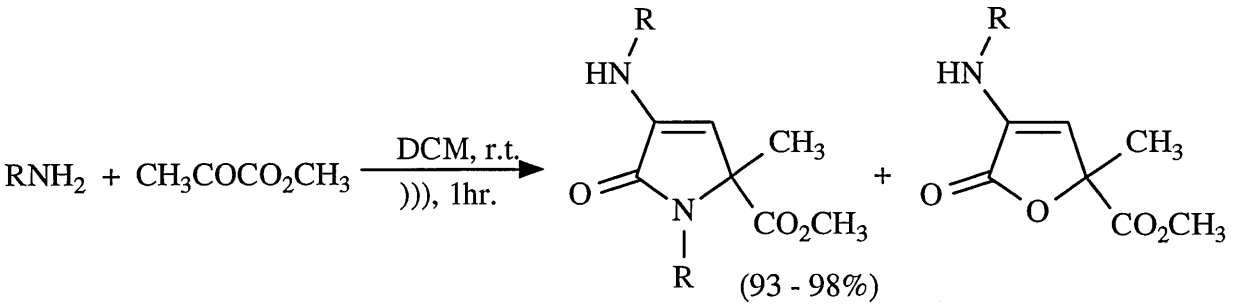
R = Me, t-Bu X = S, NH

Solvent = Acetonitrile; yield = stir <8%,))) <32%

Toluene; yield = stir <75%,))) 92%

[Scheme 14]

Primary amines react with methyl pyruvate to form 2-oxo-3-pyrrolines (**29**) in good yield under sonication[114] with short reaction times and mild conditions. The quiet equivalent requires 8-10hrs of reflux. Under certain conditions the related γ-lactone may be produced in significant amounts [Scheme 15].

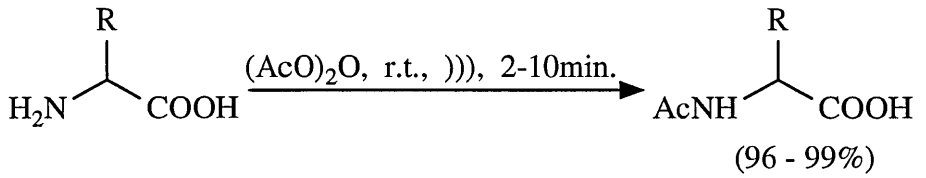


(29)

R = $C_6H_5CH_2$, C_6H_5, *p*-$CH_3C_6H_4$, *p*-ClC_6H_4, *p*-$CH_3CONHC_6H_4$

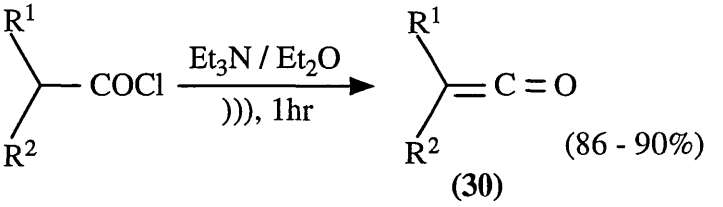
[Scheme 15]

A rapid sonochemical preparation (2-10 minutes) of N-acetylamino acids from the amino substrate at ambient temperature with acetic anhydride and water has been described[115] as giving quantitative yields and proceeds without racemisation. Conventional methods require more vigorous conditions which lead to racemisation.

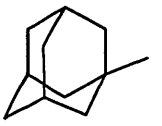
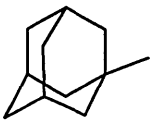
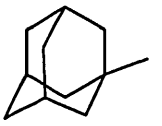


Ketene Synthesis

The dehalogenation of α-haloacetyl halides or the dehydrohalogenation of the appropriate substituted acetyl halides can be used to prepare ketenes. When substrates substituted with bulky groups are used it is difficult to obtain good yields of ketenes. However satisfactory yields can be achieved when sonication is used[116,117] e.g. the synthesis of di-tert-butyl-, di(1-adamantyl)- and (1-adamantyl)-tert-butylketenes **(30)** through the dehydrochlorination of the corresponding acetyl chlorides with triethylamine under ultrasonic irradiation [Scheme 16]. The sonicated reactions gave a ketene yield of 86-90% compared to the quiet reactions yield of <10%.



(30)

	R1	R2
A:		
B:		t-butyl
C:	t-butyl	t-butyl

[Scheme 16]

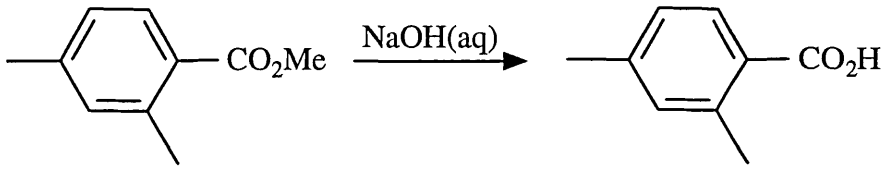
1.3.2 Heterogeneous Systems: liquid/liquid

Generally speaking these reactions are organic-aqueous biphasic systems which benefit from the emulsifying effect that ultrasonic waves create. Emulsification arises from cavitation at the boundary of the two phases and the microstreaming effect of ultrasound. Emulsification of immiscible liquids increases their contact area and hence reaction rate[118]. This effect enhances the action of phase transfer catalysts or even makes them redundant.

Bimolecular Reactions

Hydrolysis

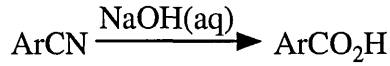
Ester hydrolysis can be conducted under milder conditions when ultrasound is applied to the system. The alkaline hydrolysis of methyl-2,4-dimethylbenzoate[119] to the acid is an example where ultrasound has reduced reaction time and increased yield by emulsifying the reagents efficiently [Scheme 17].



Conditions	Time (min)	Yield
Reflux	90	15
))), r.t.	60	94

[Scheme 17]

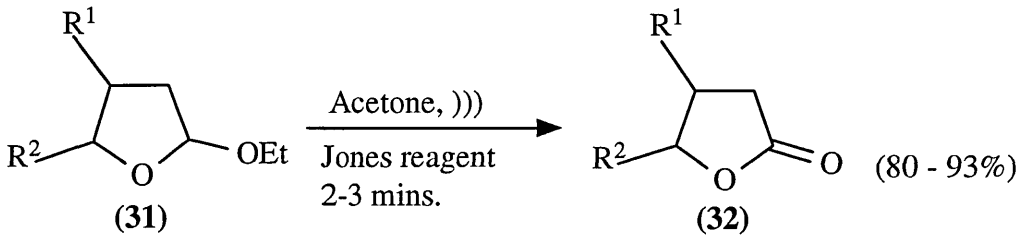
These conditions can also accelerate the hydrolysis of triglycerides such as glycerol tripalmitate, which benefits[120] from the application of ultrasound. Ultrasound also improves the yields of basic hydrolysis of nitriles to the resultant acid. In the sonicated reaction[121], phase transfer catalysts are not required [Scheme 18].



Conditions	Ar	Time/h	Yield (%)
r.t., stir	Ph	10	15
r.t.,)))	Ph	10	33
Reflux, stir	Naphthyl	6	63
Reflux,)))	Naphthyl	6	98

[Scheme 18]

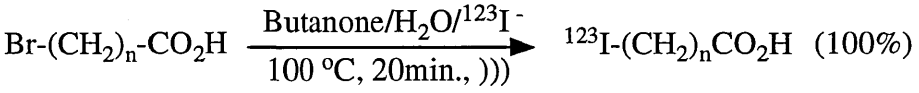
It was found[122] that several 2-alkoxytetrahydrofurans **(31)** could be converted very rapidly to the resultant γ-butyrolactones **(32)** by Jones reagent while under sonication. Conventional conditions produce good yields but take one to several hours for the hydrolysis to be complete. Sonochemical irradiation of the hemiacetal **(31)** in acetone and two to three equivalents of 1.6M Jones reagent resulted in the formation of γ-butyrolactones **(32)** in good yields within two to three minutes.



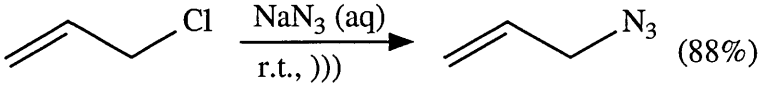
The authors do not propose why this reaction is accelerated but it will probably be due to the mass transport and efficient mixing properties of ultrasound.

Substitutions

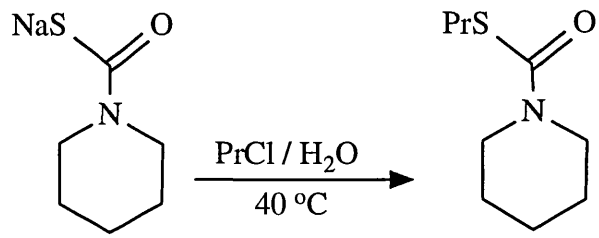
Mertens *et al*[123] have successfully transformed a ω-bromo fatty acid to its ^{123}I-analogue *via* a Finkelstein exchange reaction. This radioisotope is expensive, short-lived, thermally unstable, and requires anhydrous conditions for its preparation. Ultrasound has reduced the preparation time (20 mins) temperature (originally 180 °C) and the reaction can tolerate greater amounts of water.



Bromoacetonitrile, allylic and propargylic halides can be easily substituted[124] with aqueous sodium azide when the reaction is sonicated. The yield is maximised since the product's density is such that it floats to the surface of the reaction, where it is unaffected by degradation.



Another reaction which benefits from the action of ultrasound[125] is the alkylation of thermally sensitive thiocarbamic acid salts **(33)** to the product **(34)** [Scheme 19]. This reaction proceeds much slower than its stirred equivalent which is insensitive to the rate of stirring, which suggests that ultrasound is aiding the reaction by a mechanism other than mechanical means. The authors suggest activation of the alkyl halide, *via* a free radical process. Further research[125] has compared the yield of the stirred and sonicated reaction with the yield obtained when the reaction is subjected to acoustic waves emitted from a rotor type emitter [Scheme 19].

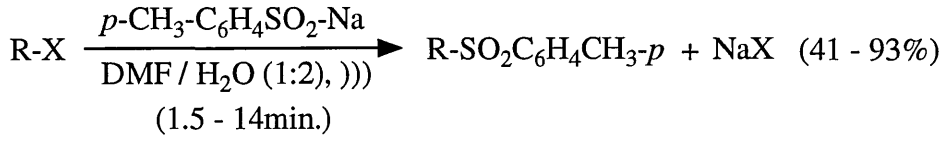


(33) **(34)**

Conditions	Time/ min	Yield (%)
Stir	60	<10
Rotor	60	50
)))	40	100

[Scheme 19]

A simple preparation of sulfones from alkyl halides and sodium *p*-toluenesulfinate in DMF/water at room temperature[126] has been carried out. The reaction time is very short and moderate to good yields are obtained [Scheme 20].



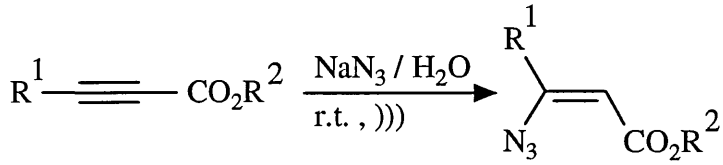
X = I, Br, Cl

R = Me, Et, Pr, Benzyl, *p*-$BrC_6H_4COCH_2$-, allyl, ester, cyclic groups.

[Scheme 20]

Additions

Priebe[127] has successfully added sodium azide to several alkynoate esters **(35)** to form the azide **(36)**. Using sonication good yields and selectivity are obtained [Scheme 21].

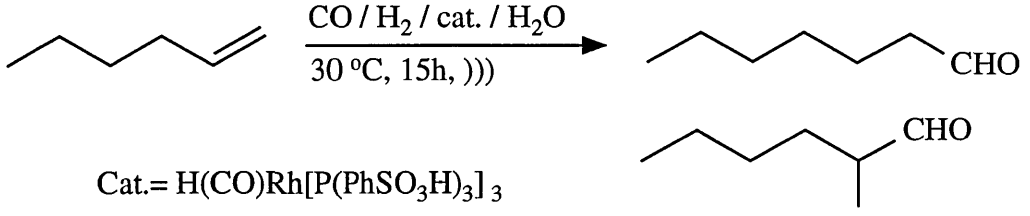


(35) **(36)**

R^1 = H R^2 = Me, CH_2Br (62 - 86%)

[Scheme 21]

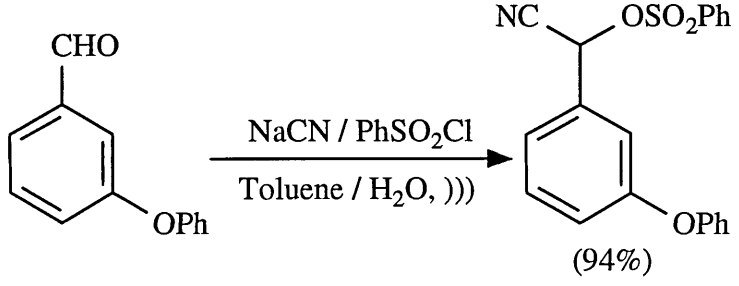
Aldehydes can be hydroformylated from olefins[128,129] using a complex system of 1-hexane, water and a soluble catalyst [Scheme 22]. This system is sonicated under a stream of carbon monoxide and hydrogen to produce a mixture of heptanal and 2-methylhexanal with a rate 2-3 times higher than the quiet reaction.



Cat.= $H(CO)Rh[P(PhSO_3H)_3]_3$

[Scheme 22]

Carbonyl compounds can undergo addition reactions[130] such as hydrocyanation of 2-phenoxybenzaldehyde. The formyl group reacts with aqueous sodium cyanide in the presence of benzenesulphonyl chloride in toluene solution to form the cyanohydrin sulphonate ester in good yield (94%). When the reaction is quiet the yield decreases (40%).



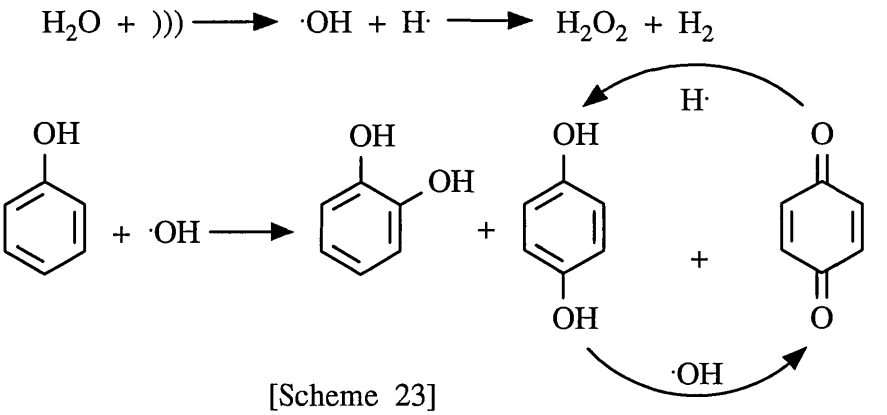
Sonolysis of Aqueous Solutions

The sonolysis of 3-chloropropionitrile and water in a biphasic system [131] was found to react to produce the corresponding amide at room temperature. Yields and a comparison with a stirred reaction were not given.

$$ClCH_2CH_2CN \xrightarrow{H_2O,))),\ r.t.} ClCH_2CH_2CONH_2$$

A comprehensive kinetic and mechanistic study has been carried out on the sonochemical oxidation of phenol[132] at various pHs to form catechol, hydroquinone and benzoquinone in air-equilibrated aqueous media [Scheme 23]. The ratios of the products were dependent on the conditions that were used.

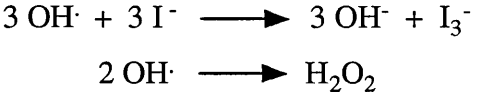
The authors confirm that hydroxyl radicals play a major role in the sonochemical oxidation of the phenol. This is an interesting study but the rate of decomposition (μM scale) will limit the application of this reaction.



[Scheme 23]

Ultrasound has also been utilised in the degradation of dichlorobenzene and aromatic hydrocarbons such as anthracene and pyrene in aqueous systems[133], with the obvious environmental application of the purification of water. The authors used these compounds as a model for what may happen if polychlorinated biphenyls (PCBs) were subjected to the same conditions. It was suggested that the compounds were degraded to volatile material that could not be detected by the methods used. However there is no firm proposal as to what products were made from the sonochemical destruction of these compounds.

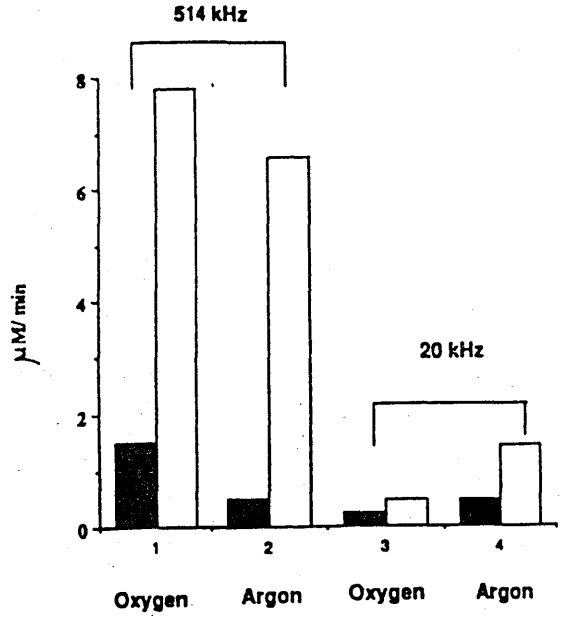
Frequency and the dissolved gas has been found to have an effect[134] on the rate of oxidative processes from radicals induced by ultrasound. It was found that the oxidation rate of iodide ion oxidation to tri-iodide and hydrogen peroxide production under argon and oxygen were greater at 514kHz ultrasound than at the commonly used frequency 20kHz [Scheme 24].



[Scheme 24]

It was also found at the higher frequency oxygen increases the rate over argon whereas at the lower frequency argon had the highest rate [Figure 1.14].

Figure 1.14 Tri-iodide and Hydrogen Peroxide Formation[134]



Black bar = rate of formation of triiodide in KI, 10^{-2}M solution; Clear bar = rate of formation of hydrogen peroxide

The effects are associated with the sonolysis of water into hydroxyl radicals and hydrogen atoms and their resultant recombination or oxidation of other species. The authors rationalise the effects observed by the shorter time period in which the cavitational bubble exists, 3 x 10^{-7}s at 514kHz & 10^{-5}s at kHz. They postulate that at the higher frequency and shorter bubble duration any OH· radical formed will have a greater chance of escaping the bubble before it recombines. This increases the chance of the hydroxyl radical reacting with the relevant species and thus increasing reaction rate. The difference between the gases at the different frequencies can be explained by molecular oxygen scavenging the hydrogen atoms forming ·OOH radicals and lowering the recombination of ·OH and ·H radicals, therefore allowing more ·OH radicals to escape from the bubble (high frequency) [Scheme 25].

$$H\cdot + O_2 \longrightarrow \cdot OOH$$
$$H\cdot + \cdot OH \longrightarrow H_2O$$

[Scheme 25]

However low frequency and higher residence time in the cavitation bubble allows the hydroxyl radical to be scavenged by the hydroperoxy radical ·OOH.

Consequently at the lower frequency argon has the higher rate of formation of H_2O_2 and I_3^-.

$$\cdot OH + \cdot OOH \longrightarrow H_2O + O_2$$

1.3.3 Heterogeneous Systems: Solid-Liquid

This section will cover non-organometallic heterogeneous solid-liquid reactions. These systems involve reagents of low solubility which can in turn result in slow rate and reduction of selectivity. This can be resolved in certain cases with the application of ultrasound. These reactions fall into two general categories, dispersion and consumption of the solid, and reaction of the reactants on the surface of a hard solid reagent that does not disperse.

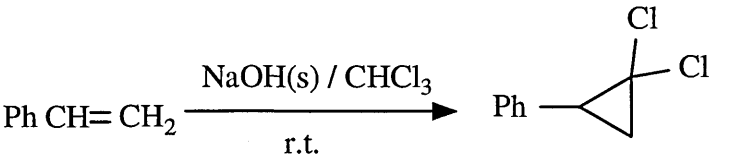
1.3.3.1 Dispersion of Reagent

Here the insoluble reagent is broken up and dispersed within the reaction and is consumed.

Inorganics

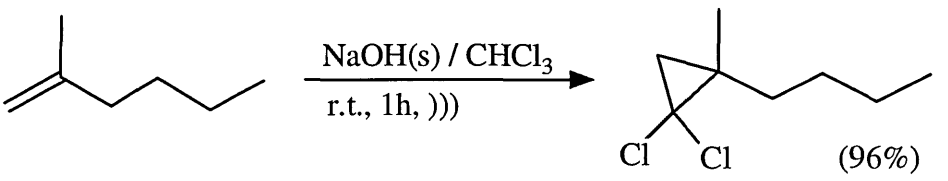
Bases

Many inorganic bases such as sodium or potassium hydroxide are used with phase transfer catalysts in heterogeneous reactions. The mass transport properties of ultrasound and its ability to break up friable solids make it ideal for such systems. The formation of dihalocyclopropanes **(37)** and **(38)** has been greatly improved by the use of ultrasound[135,136], and this work illustrates how ultrasound on its own may not improve the yield, but when ultrasound and stirring is used the rate and yield can be greatly enhanced [Scheme 26]. Effects such as these arise from a system where the ultrasonic intensity is insufficient to stir the solution efficiently (US bath in this case) and the use of a dense organic phase (chloroform).



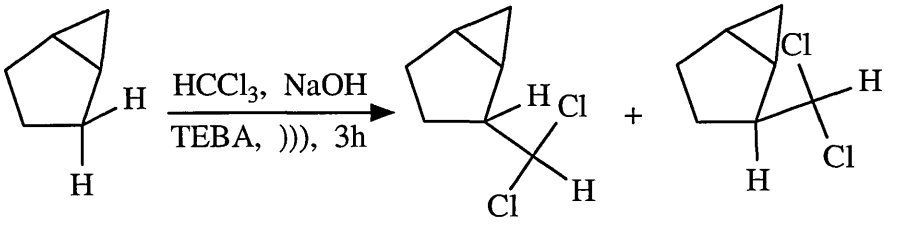
(37)

Conditions	Time / h	Yield (%)
Stir +)))	1	96
)))	20	38
Stir	16	31



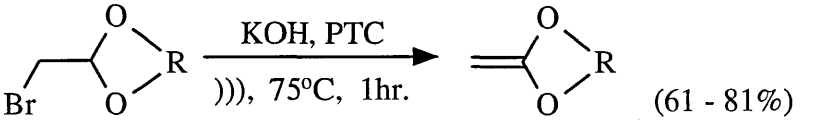
[Scheme 26] **(38)**

In a similar experiment selective insertion of dihalocarbenes into carbon-hydrogen bonds adjacent to cyclopropane rings **(39)** to form the compounds **(40)** and **(41)** was carried out under ultrasound[137] in chloroform with powdered sodium hydroxide and phase transfer catalyst (triethylbenzylammonium chloride (TEBA)).



(39) **(40)** 83% (4.3:1) **(41)**

Phase transfer catalysts (tetrabutylammonium bromide (TBAB) or Aliquat^{R} 336) have been used in conjunction with ultrasound[138] in the preparation of cyclic ketene acetals **(42)** *via* β-elimination without solvent [Scheme 27]. It was found that ultrasound enabled the reaction to proceed without solvent allowing the product to be distilled directly from the reaction mixture at reduced pressure. When the PTC was absent from the reagents, the reaction still proceeded but the yield was reduced. The authors believe this illustrates that the transfer of the hydroxide ion to the organic phase is necessary for high yields.



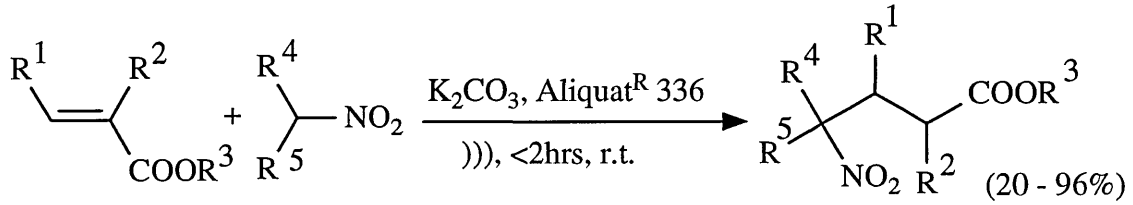
(61 - 81%)

(42)

R = $-(CH_2)_2-$, $-CHPh-CH_2-$, $-(CH_2)_4-$, $-CH_2CHCHCH_2-$, C_6H_{12}

[Scheme 27]

Aliquat^R 336 and ultrasound have also been used in a reaction[139] without solvent using potassium carbonate as the base catalyst in the addition of nitroalkanes to monosubstituted α,β-unsaturated esters. This Michael addition occurs rapidly (<2hrs.) without solvent and a with cheap base to give a good yield of the product **(43)** [Scheme 28]. When the phase transfer catalyst was removed, no reaction occurred, and when ultrasound was not applied the reaction was still observed but was much slower (2 days). These observations suggest ultrasound is having a mechanical effect on the potassium carbonate i.e. breaking up the structure into smaller pieces and thus increasing reaction rate, in addition to the beneficial effects of mass transport of reactants.



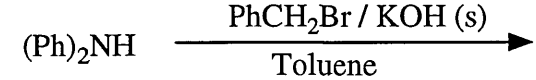
(43)

R^1 = Me, Ph, H, CO_2Me R^2 = H, CH_2CO_2Me R^3 = Me, CH_2Ph

R^4 = H, Me R^5 = Me, Et

[Scheme 28]

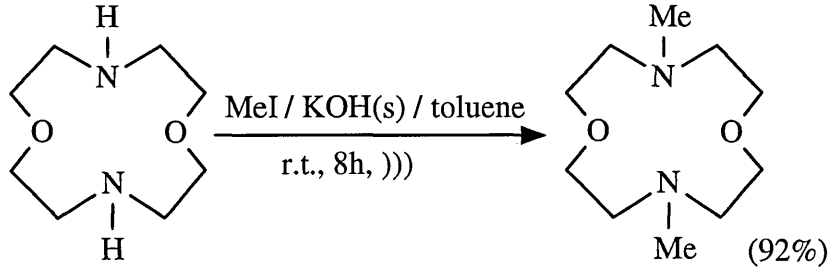
It has been shown[140], although a phase transfer catalyst was used (polyethyleneglycol methyl ether), that by sonicating a toluene solution of solid potassium hydroxide and methyl iodide several secondary amines can be alkylated [Scheme 29]. The results show excellent improvements in reaction rate, illustrating the efficiency of the dispersion of KOH and mass transport.



Conditions	Time / h	Yield (%)
Reflux, stir	48	70
)))	1	98

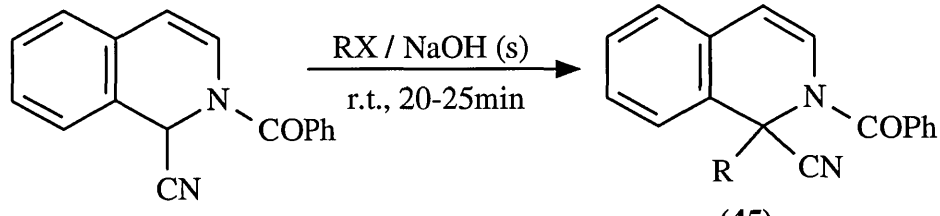
[Scheme 29]

Other N-alkylations have been carried out[141] where crown compounds have been alkylated effectively to the product **(44)** with sonicated methyl iodide and potassium hydroxide in toluene.



(44)

There have also been reports of C-alkylations[142] as well as N-alkylations, where the reaction rate of alkylation of a dihydroisoquinoline to the product **(45)** was moderately accelerated [Scheme 30].



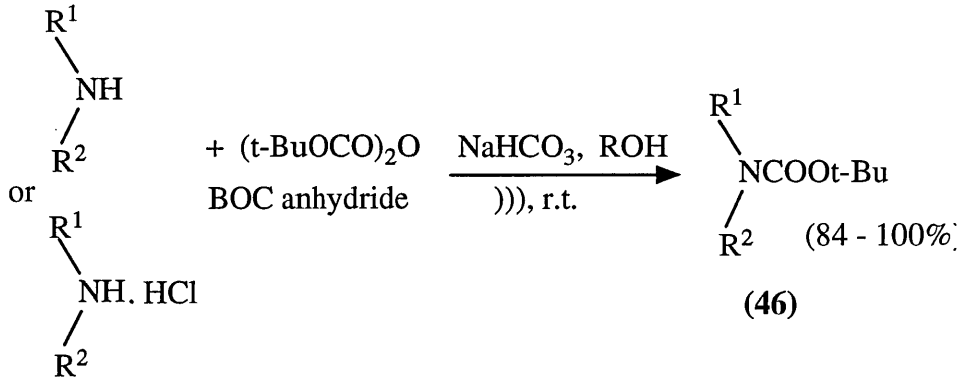
(45)

R	Conditions	Yield (%)
$PhCH_2$	Stir	50
$PhCH_2$	)))	60
$4\text{-}ClC_6H_4CH_2$	Stir	26
$4\text{-}ClC_6H_4CH_2$	)))	50

[Scheme 30]

The protection of amines with the tert-butyloxycarbonyl group is often carried out under basic conditions with BOC anhydride. The reactivity of the anhydride and reaction rate are sometimes unsatisfactory with expensive derived reagents required in such cases. With sonication many of these problems are solved with the reaction occurring efficiently using the standard reagent under sonication. The reaction[143,144] can be carried out in methanol or ethanol with sodium carbonate or bicarbonate as the base, and work up is a simple operation of filtration and evaporation to yield the pure product **(46)** [Scheme 31]. The authors state sonication has only a mechanical effect

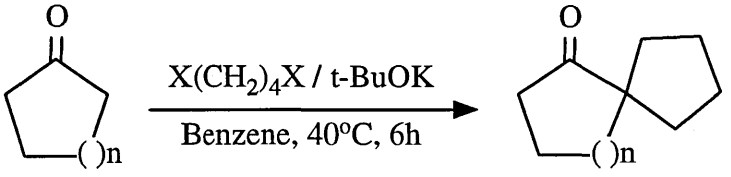
on this reaction. The method can also be used with amine salts as the starting material which avoids the step of amine "liberation".



(46)

[Scheme 31]

The yield of spiro ketones **(47)** from cycloalkanones[145] was also increased dramatically with the application of ultrasound [Scheme 32].

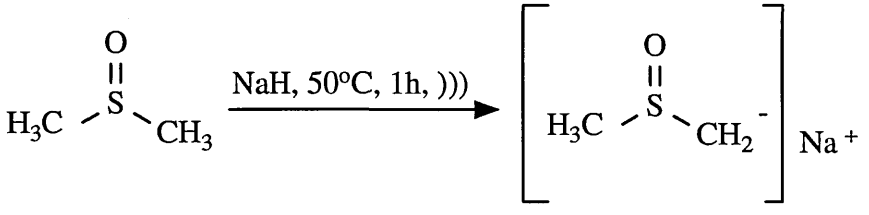


(47)

n = 1, 2 Stir 14 -28%))) 70 - 90%

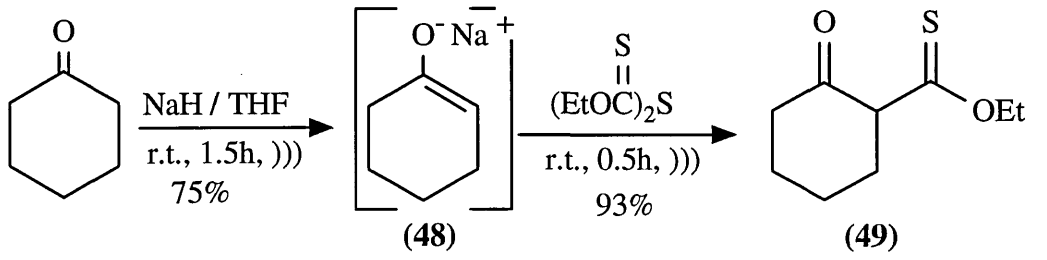
[Scheme 32]

Hydrides can also benefit from the application of ultrasound, both in the preparation of reagents and synthesis. Sodium methylsulfinylmethylide can be prepared by reacting sodium hydride with dimethyl sulphoxide.



The preparation involves a narrow temperature range and the resultant reagent has restricted stability. When ultrasound (800kHz) is used[146] the preparation is carried out over one hour at 50 °C, and the resultant reagent has an extended period of stability. Sodium hydride and ultrasound[147] can also be used to prepare ketone

enolate **(48)** which is then used in a sonicated condensation reaction with a trithiodicarbonate to give the resultant β-keto-thienoester **(49)**. Again the enolisation step is improved by ultrasound (75% yield) over the quiet reaction (18% yield).



(48) **(49)**

Zinc borohydride can be used to selectively reduce carboxylic ester groups to alcohol groups[148] under sonication. This is a reaction that does not proceed when ultrasound is absent. It is found that aliphatic ester groups are reduced while aromatic ester groups are unreactive [Table 1.2]. The addition of an electron transfer agent, N,N-dimethylaniline allows the reduction of the aromatic esters to proceed, which further strengthens the argument of the connection between ultrasound and electron transfer.

Table 1.2

		With N,N-dimethylaniline
Ester	% Reduction (hrs)	% Reduction (hrs)
Methyl cyclohexane-carboxylate	100 (24)	100 (14)
Methyl phenyl acetate	100 (18)	100 (12)
Methyl benzoate	0 (24)	100 (24)
Methyl4-chlorobenzoate	0 (24)	100 (24)

Other Inorganics

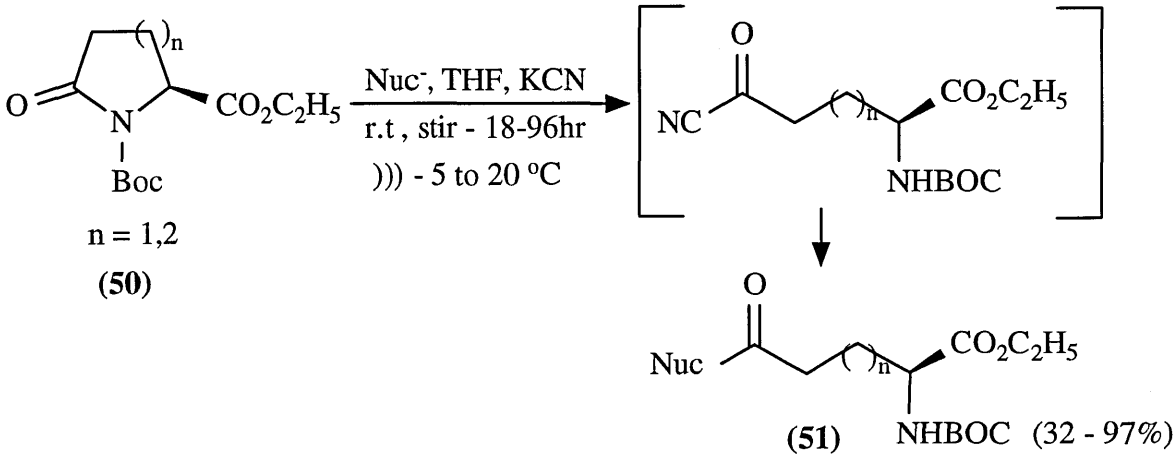
Ultrasound allows the use of potassium cyanide for the synthesis of acyl cyanides at lower temperatures[149], where conventional methods require the use of silver, copper or thallium salts [Scheme 33]. One obvious advantage is the economic one.

$$RCOCl \xrightarrow[50^{\circ}C,\ 1\text{-}3h,\ )))]{KCN\ /\ CH_3CN} RCOCN \quad (65 - 85\%)$$

$R = 2\text{-}CH_3C_6H_4$, $4\text{-}CH_3C_6H_4$, furyl, Ph

[Scheme 33]

The potassium cyanide catalysed regioselective ring opening of chiral N-BOC protected pyroaminoadipate and pyroglutamate ethyl ester **(50)** with heteronucleophiles to the open chain product **(51)** was found to proceed in good yield, but suffered from long reaction times which was believed to be due to the low solubility of KCN in the reaction medium (THF). Ultrasound was successfully used[150] to disperse the KCN and increase the reaction rate [Scheme 34]. The regioselectivity was explained by nucleophilic attack of the cyanide ion on the amide carbonyl group to produce an acyl cyanide intermediate.



n = 1,2

(50)

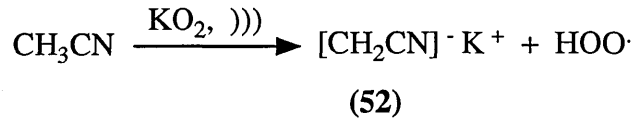
$Nuc^- = HC{\equiv}CCH_2OH$, $H_2C{=}CHCH_2OH$, $PhCH_2OH$

p-$MeOC_6H_4CH_2OH$, $H_2C{=}CHCH_2NH_2$, $PhCH_2NH_2$, $PhCH_2SH$

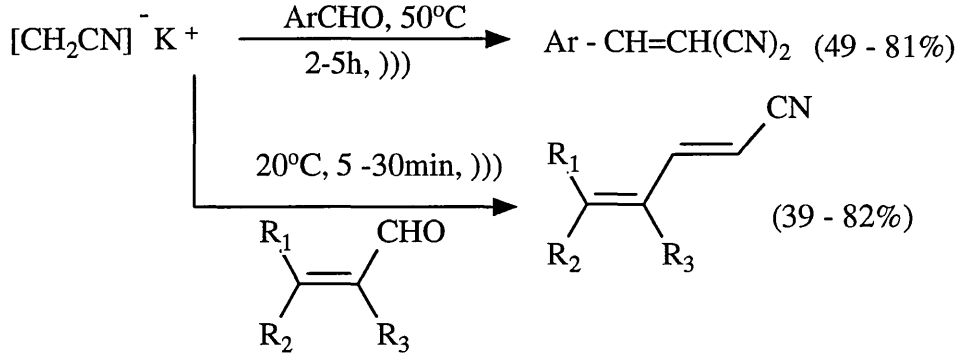
[Scheme 34]

The preparation of the anion of acetonitrile **(52)** using potassium superoxide, is facilitated with the use of ultrasound. The initial step involves a radical anion reaction[151] which is accelerated by the free radical promoting character of ultrasonic

waves [Scheme 35]. This anion can then be used in a condensation reaction with various aldehydes. These reaction are also accelerated with the use of ultrasound.

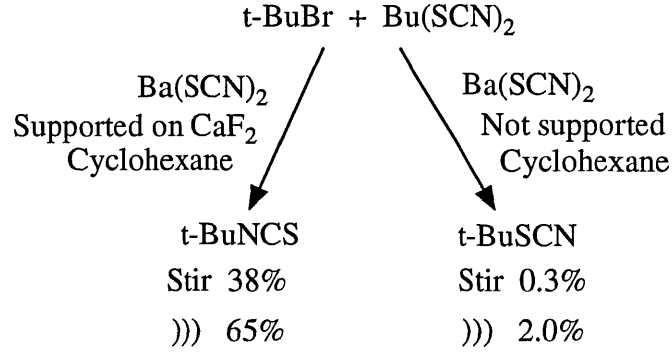


(52)



[Scheme 35]

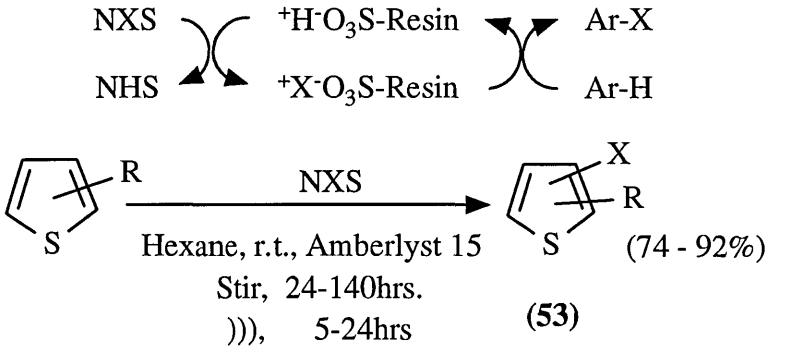
Ultrasound is found to increase the yield[152] in the thiocyanation of t-butyl bromide with $Bu(SCN)_2$ in cyclohexane. This reaction exhibits the unusual feature of the reaction pathway being altered very significantly when the reagent is supported on calcium fluoride. When $Ba(SCN)_2$ is supported on solid CaF_2, N-selectivity predominates and t-BuNCS is produced in high yield; whereas unsupported $Ba(SCN)_2$ favours S selectivity and t-BuSCN in low yield [Scheme 36]. The mechanism is not understood.



[Scheme 36]

Halogenation

Ultrasound was found to promote the electrophilic halogenation of aromatics and heteroaromatics[153] in a two phase hexane/solid N-halosuccinnimide (NXS) which was catalysed by strongly acidic sulphonated resin Amberlyst^R 15. Ultrasound accelerated the reaction rate by up to ten times and it was also found that almost the same yields could be obtained without the catalyst when the reaction was sonicated. The acid catalyst is thought to protonate NXS then transfer the halogen atom to aromatics in a catalytic manner; ultrasound appears to transfer the halogen directly. For example, in the synthesis of disubstituted thiophenes **(53)** [Scheme 37].



R = 2-Me, H, 2-Br, 3-Br, 2-Cl

X = Br, Cl

[Scheme 37]

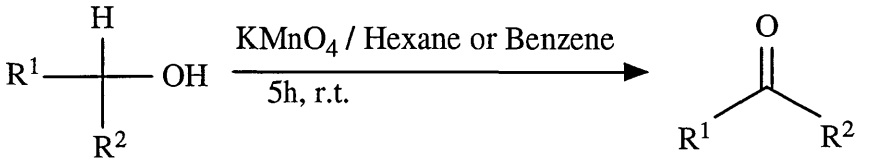
1.3.3.2 Surface Reactions on Hard Solids

This section deals with "hard reagents" which are not broken up by cavitation. The reagent is either consumed by the reaction or it exhibits catalytic character and remains unchanged. The effect of ultrasonic waves in this case is to "scour" the surfaces effecting desorption i.e. the cleaning effect of surfaces that can arise from cavitation and or microstreaming.

A) Systems Which Consume the Solid

Oxidation and Reduction Reactions

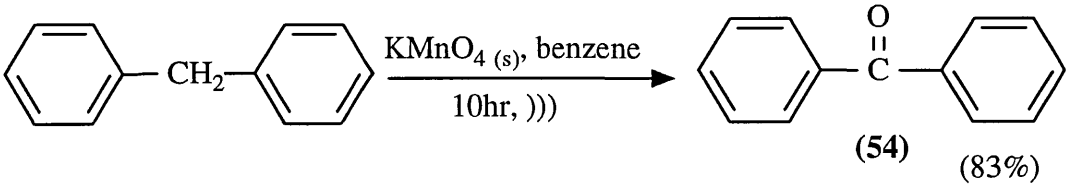
In these types of reactions the main advantage of ultrasound is to allow the worker to experiment with alternative solvents or stoichiometry e.g. the ability to dispense with having to use water as a co-solvent in oxidation which can decrease yields and complicate the work up procedure. For example, solid potassium permanganate can be dispersed[154,155] in benzene or hexane in the oxidation of alcohols [Scheme 38].



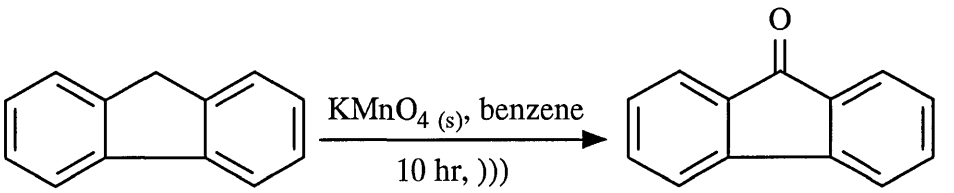
e.g. $R^1 = CH_3(CH_2)_5$, $R^2 = CH_3$: Stir (2%),))) (92%).

[Scheme 38]

Solid $KMnO_4$can be used in sono-oxidation of activated methylenes[152] into the corresponding ketones **(54)** and **(55)**. Diphenylmethane and fluorene both give good yields of benzophenone and fluorenone respectively [Scheme 39].



(54) (83%)
(cf. 27% stir)



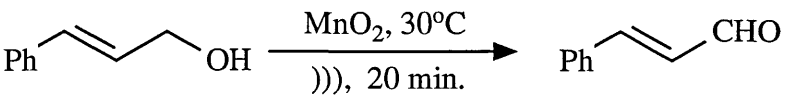
(55) (69%)
(cf. stir - no reaction)

[Scheme 39]

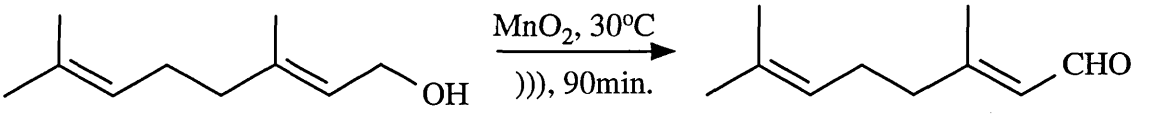
Increased dissolution of solid $KMnO_4$ does not occur with sonication which is evident by the lack of the characteristic colour of potassium permanganate in solution. Rather the increased reactivity of the $KMnO_4$ stems from a fine powder that is formed on the surface of the $KMnO_4$ when exposed to ultrasound, which can be observed from scanning electron micrographs. This is illustrated by pre-sonicating the $KMnO_4$ which allows the oxidations to be accelerated in a conventional quiet reaction. Ultrasound, therefore, increases the number of active sites[152] on the solid $KMnO_4$.

Similarly, oxidations of unsaturated alcohols with manganese dioxide are improved since ultrasound activates crystalline manganese dioxide[156,152] which otherwise is of low reactivity. This oxidation usually requires excess reagent and reproducibility depends on the preparation of the manganese dioxide. Using scanning electron micrographs of the MnO_2 surface it has been shown that ultrasound modifies the

surface of the MnO_2 by exposing active sites. Whatever the mechanism of activation the resulting reagent oxidises cinnamyl alcohol, geranoil and 1-phenylethanol[157], also the use of a less volatile solvent accelerates the oxidation [Scheme 40].



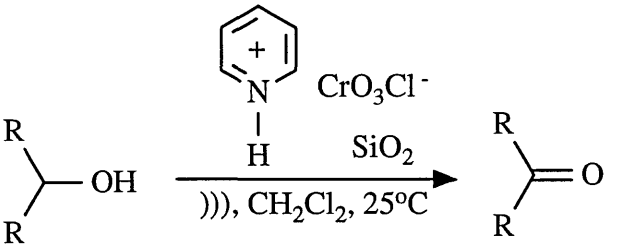
Solvent	Yield (%)
Pentane	44
Hexane	51
Octane	73



Solvent	Yield (%)
Heptane	48
Octane	80

[Scheme 40]

The conversion of alcohols to carbonyl compounds using pyridinium chlorochromate (PCC) has been improved[158] with the application of ultrasound. Ultrasound was used to activate the surface of both the silica gel (which acts as an absorbent for unwanted by-products) and the oxidant. It was found that the yield was improved only slightly, but the ultrasound promoted reaction required less PCC (1.2 - 1.5 equiv) than the conventional method (1.5 - 2.0 equiv) and the reaction times were reduced [Scheme 41].



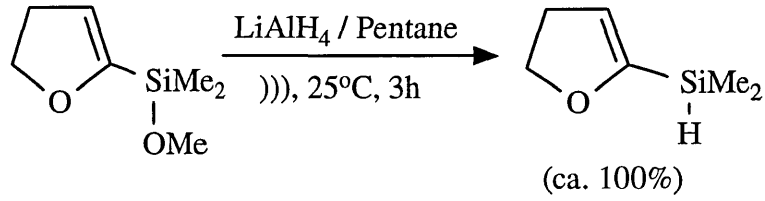
[Scheme 41]

Lithium aluminium hydride can be used to reduce several heteroatom - halogen bonds[159] in solvents such as hexane or cyclohexane [Scheme 42].

$$R_3MCl \xrightarrow[\text{))), 25 - 40°C, 2.5 - 4.5h}]{LiAlH_4 \text{ / Alkane}} R_3MH \quad (80 - 95\%)$$

$R = CH_3, CH_2CH_3$

$M = Si, Ge, Sn$



(ca. 100%)

[Scheme 42]

In dimethoxyethane solution aromatic halides undergo substitution by a hydride[160]. This reaction would be difficult under conventional conditions. Interestingly the vapour pressure effect was shown here when the more volatile THF proved to be a less efficient medium [Scheme 43].

$$ArX \xrightarrow[\text{4 - 5h,)))}]{LiAlH_4 \text{ / DME, } 35°C} ArH \quad (98\%)$$

$Ar = 2\text{-}CH_3C_6H_4, 2\text{-}MeOC_6H_4, 3\text{ - }ClC_6H_4$

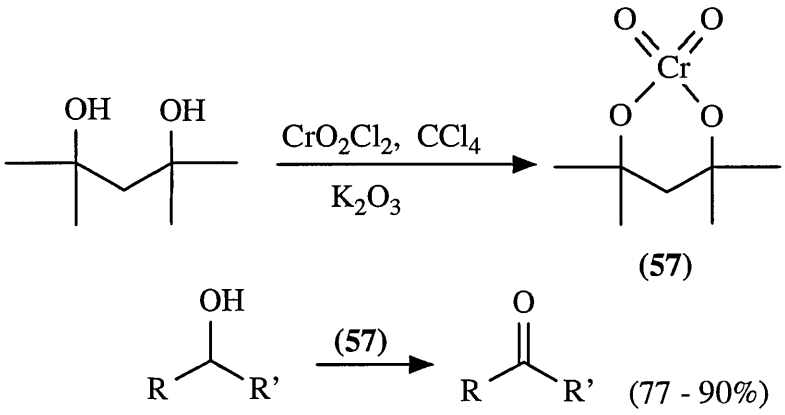
$X = Br, I$

[Scheme 43]

Ultrasound has been used successfully[161] in the preparation of chromyl chloride **(56)**, which is used to prepare chromate esters **(57)** as oxidation reagents [Scheme 44]. The rate acceleration is explained by ultrasound activating the chromium trioxide particles by localised erosion and microfragmentation, and the solubilisation of the reagents.

$$2CrO_3 + TiCl_4 \xrightarrow[\text{2 - 3hr,))), r.t}]{CCl_4 \text{ or } CH_2Cl_2} 2\ Cl\text{–}\overset{\overset{O}{\|}}{\underset{\underset{Cl}{|}}{Cr}}\text{=}O + TiO_2\downarrow$$

(56)



R' = H, Alkyl

R = CH_3, Ph, n-C_6H_{13}, t-Bu

[Scheme 44]

Ultrasound was used in the oxidation of benzylic C-H using chromyl chloride in an Etard oxidation. Ultrasound was also used to hydrolyse the resultant intermediate to the ketone, with a 2-fold acceleration of the reaction rate. The homogenisation and mixing properties of ultrasound is considered to accelerate this two phase hydrolysis step.

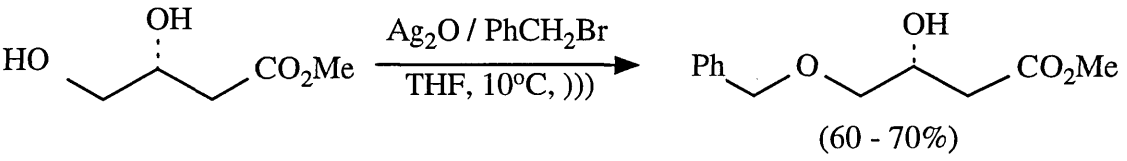
$$CrO_2Cl_2 / CH_2Cl_2 \xrightarrow[0^oC,\ ))),\ 1h]{ArCH_2R\ /\ CH_2Cl_2} ArCH_2R \cdot 2CrO_2Cl_2 \xrightarrow[0^oC,\ 1h]{Zn\ /\ H_2O,\ )))} ArCOR$$

The ultrasound produced chromyl chloride was used directly without removal of titanium chloride to oxidise trans-2-octene to a mixture of 3-chloro-2-octanone and 2-chloro-3-octanone.

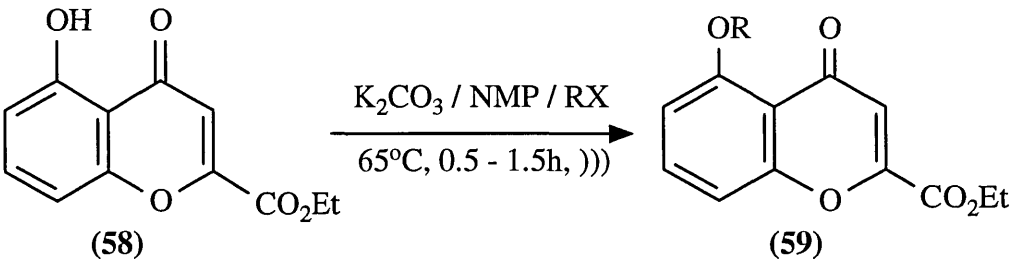
$$R'CH{=}CHR\ /\ CH_2Cl_2 \xrightarrow[)))\ 1h,\ -78^oC]{CrO_2Cl_2,\ (CH_3)_2CO} \underset{R'}{\overset{O}{\overset{\|}{C}}}\!\!-\!\!\underset{Cl}{\overset{R}{CH}} + \underset{R'}{\overset{Cl}{CH}}\!\!-\!\!\overset{R}{\overset{\|}{C}}=O$$

Substitutions

Under conventional conditions the benzylation of a primary alcohol in the presence of silver oxide occurs in low yield with poor reproducibility. When the reaction is subjected to sonication [162] improvements are made in the reaction.

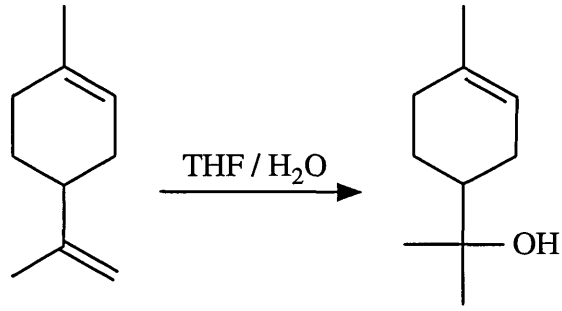


Sonication of 5-hydroxychromone **(58)** with alkyl and benzyl halides and potassium carbonate[163] produces the ether **(59)** in almost quantitative yield. Using N-methylpyrrolidone (NMP) as a solvent imparts a high amount of cavitation energy into the system, which in turn breaks up the potassium carbonate reagent.



(58) **(59)**

Oxymercuration of olefins **(60)** is a known reaction which can form carbon-oxygen bonds for the transformation of alkenes to alcohols **(61)**. Mercuric acetate or trifluoroacetate are the common reagents since other salts of mercury are not readily available. Many other mercuric salts can be prepared[164] from mercuric oxide and organic acids under sonication. The added advantage of this system is that it can be carried out as a one-pot reaction, with the salt preparation and oxymercuration proceeding simultaneously. Yields and reaction times can be improved, for example the hydration of limonene **(60)** to the alcohol **(61)** [Scheme 45].



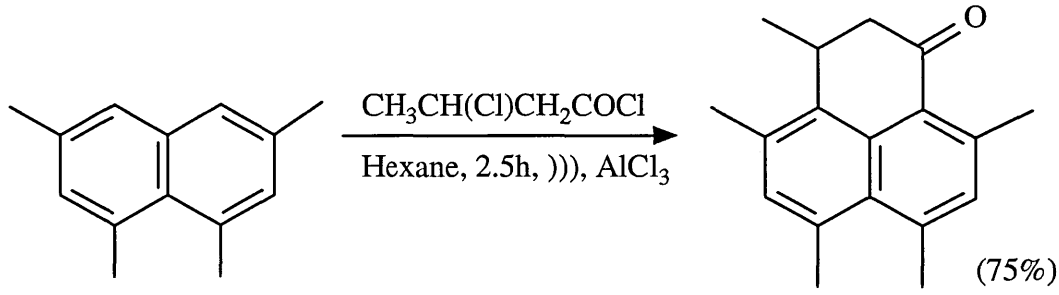
(60) **(61)**

Reagents	Conditions	Time / min	Yield (%)
$Hg(OAc)_2$	Stir	30	48
HgO / t-$BuCO_2H$	r.t.,)))	7	80
HgO / $C_7H_{15}CO_2H$	r.t.,)))	5	80

[Scheme 45]

Friedel - Crafts Reactions

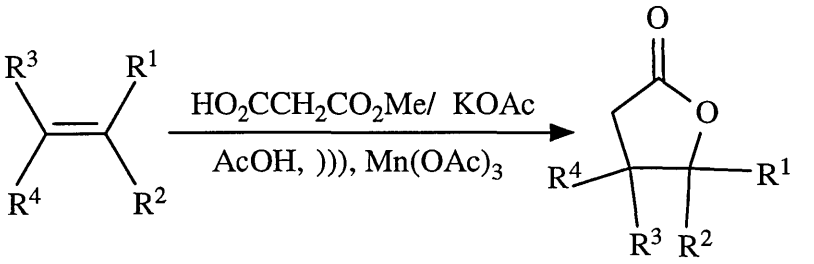
It has been reported[165] that ultrasound has a beneficial effect of reducing the particle size of the aluminium trichloride powder in the Friedel-Crafts reaction below to produce the tricyclic compound **(62)**. Sonication also has the advantageous effect of removing any unwanted oxide or hydroxide coating from the catalyst surface. Conventional methods require the use of efficient mechanical stirrers.



(62)

Olefins

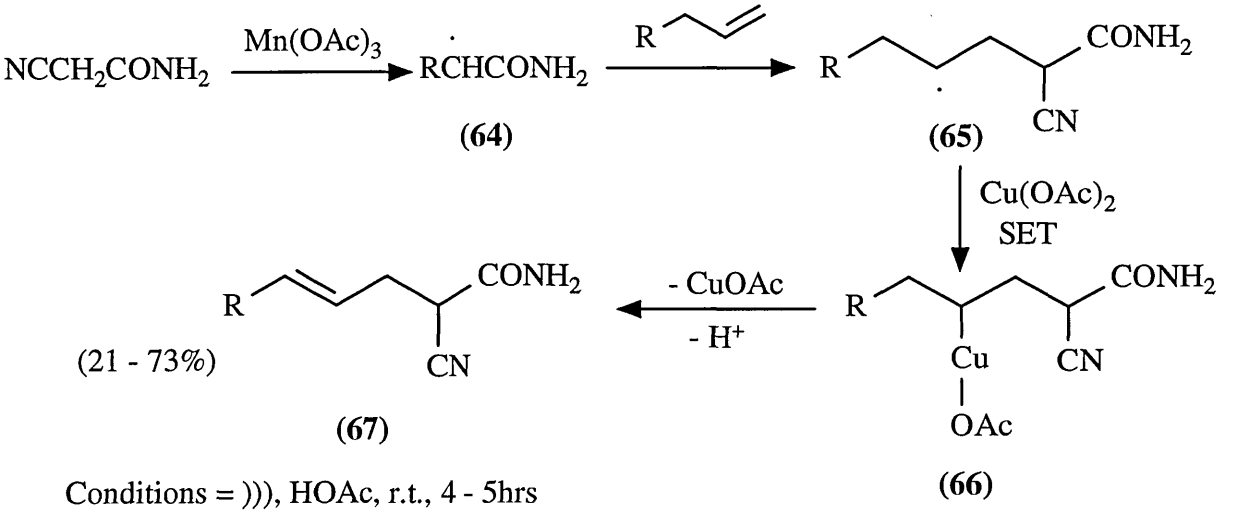
Good yields of lactones **(63)** were obtained in short reaction times from olefins using a sonicated mixture[166] of acetic acid potassium acetate and $Mn(III)(OAc)_3$ at low temperatures. The ultrasonic irradiation also reoxidised Mn(II) which allowed a catalytic amount of Mn(IV) to be used. Several olefins when used as substrates to produce substituted γ-lactones *via* a carboxyalkyl radical SET process in shorter reaction times and reduced temperature over the conventional method.



(63)

The lactonisation of olefins with the monomethyl ester of malonic acid and ceric ammonium nitrate in acetic acid and acetonitrile was found to be moderately improved[167] when sonicated. This was especially so when activated olefins such as styrene or trans stilbene were used.

Cyanoacetamide has been reacted[168] with alkyl substituted olefins in glacial acetic acid, $Mn(OAc)_3$ and $Cu(OAc)_2$ to afford γ,δ-unsaturated amides. Both the manganese and copper reagents were required to provide a satisfactory yield. The manganese extracts a hydrogen radical from the activated amide to produce the amidyl radical **(64)** which then reacts with the olefin to give the radical adduct **(65)**. This radical is then oxidised by $Cu(OAc)_2$ to give the alkyl copper intermediate **(66)**, which affords, *via* elimination, the γ,δ-unsaturated amide **(67)** [Scheme 46]. Ultrasound was found to improve the yield significantly.



Conditions =))), HOAc, r.t., 4 - 5hrs

Alkene = Hex-1-ene, hept-1-ene, oct-1-ene, dec-1-ene, cyclohexene, cyclooctene

[Scheme 46]

B) Catalytic Reagents - not consumed by system

Metallic oxides are used widely in synthesis as catalysts. Ultrasound, with its mass transport properties and surface cleaning characteristics would appear to be ideal in promoting these reactions.

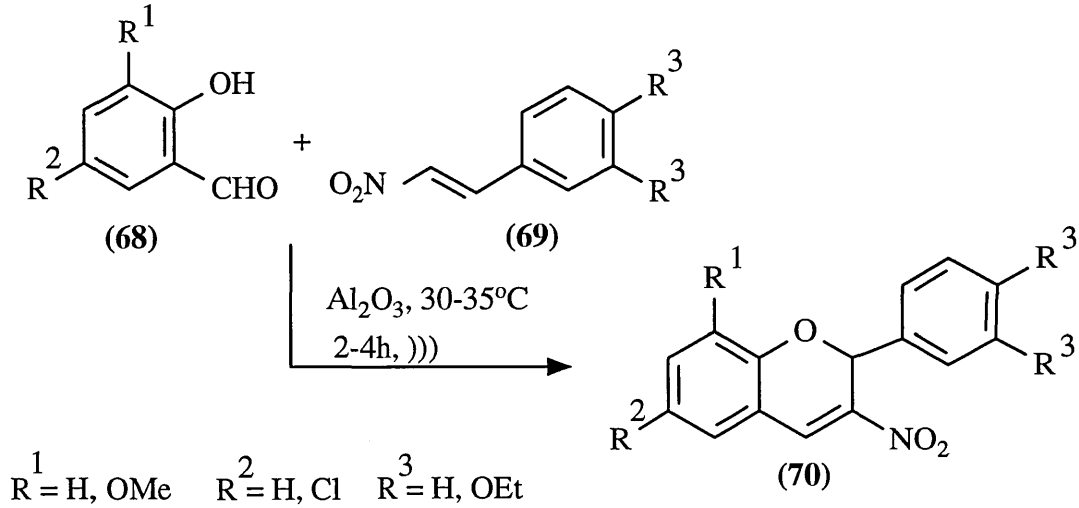
Metallic Oxides/ Acetates/ Hydroxides

The hydrosilylation of acrylonitrile to give exclusively the β-adduct using a two-component catalyst system consisting of tetramethylethylenediamine (TMEDA) and cuprous oxide[169] has been investigated. Although the sonicated reaction has a significantly higher rate than the room temperature stirred reaction, the refluxed equivalent of this reaction was found to afford higher yields. This may be due to the product being thermodynamically favoured, and the usual mass transport advantages of ultrasound being masked.

$$CH_2{=}CH\text{-}CN + R_3SiH \xrightarrow[))) \text{ or stir, or reflux}]{Cu_2O,\ TMEDA} R_3Si\text{-}CH_2CH_2CN$$

e.g. R = Cl ; stir (30%),))) (80%), reflux (95 - 100%).

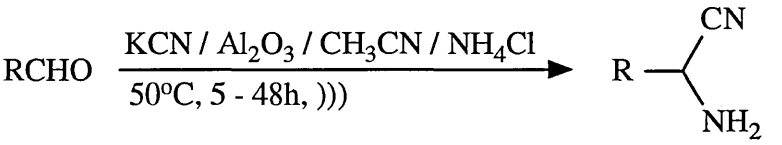
An improvement[170] on the two step condensation of substituted phenols **(68)** with nitro olefins **(69)** has been reported. This reaction is complete in 2-4hrs with good yields of the product **(70)** using alumina as the catalyst [Scheme 47].



R^1 = H, OMe R^2 = H, Cl R^3 = H, OEt

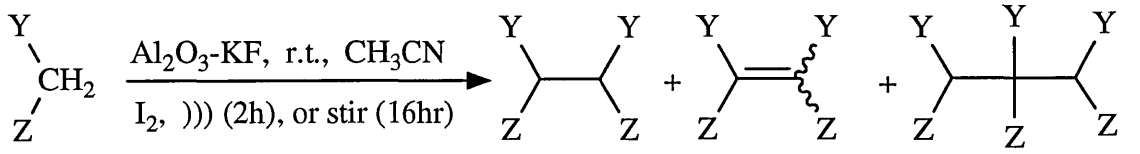
[Scheme 47]

Basic alumina has also been shown to be an effective catalyst for the synthesis of 3-nitro-2H-chromones. The yield under conventional conditions is acceptable, however the reaction time is relatively long and ultrasound[170] has reduced the reaction time to 2 hours. The method employed sonication of a solid mixture of reagents adsorbed onto alumina. This type of reaction allows a combination of the advantages of "supported reagent" processes along with sonochemical activation. A modified Strecker synthesis is another example of this effect where good yields of α-amino nitriles are obtained[171] with suppression of side reactions.



R = Alkyl, Aryl

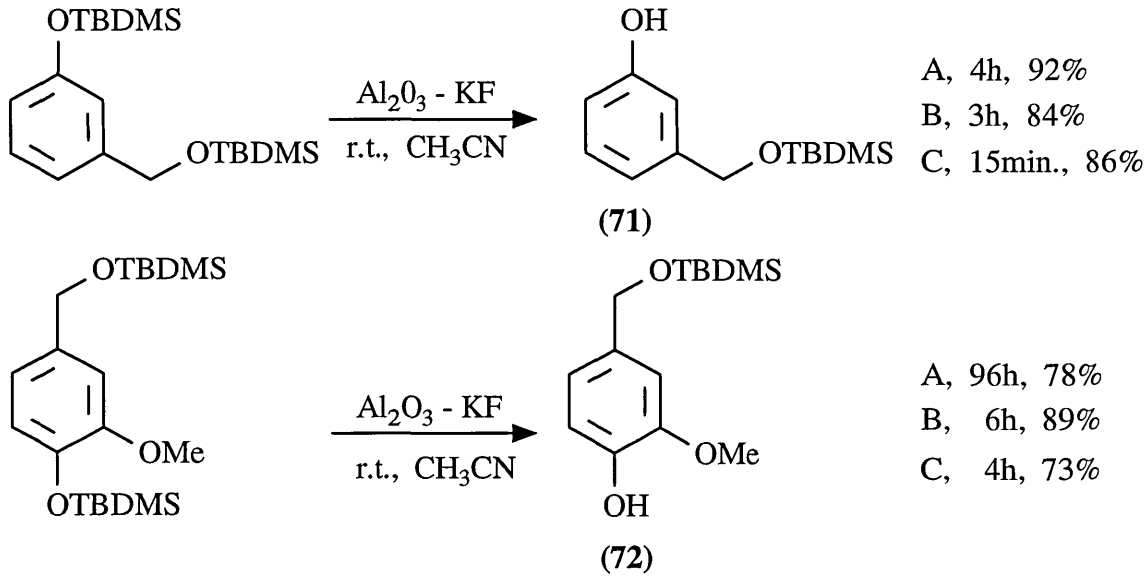
Di iodine oxidative coupling of acid carbon compounds [Scheme 48] adsorbed on potassium fluoride-alumina occurs at room temperature, but ultrasound[172] was found to improve the reaction. The authors proposed that an anion-radical mechanism, which is known to be promoted by ultrasound[173], is involved.



		Yield ii (%)	
Y	Z	Stir	)))
COOEt	COOEt	65	86
COOEt	CN	90	94
CN	C_6H_5	78	95

[Scheme 48]

The use of potassium fluoride on alumina has also been used to selectively desilylate t-butyldimethylsilyl (TBDMS) ethers of phenols[174] to the products **(71)** and **(72)**. It was found basic alumina had a higher reactivity than acidic alumina, and this reactivity was enhanced further with ultrasound [Scheme 49].

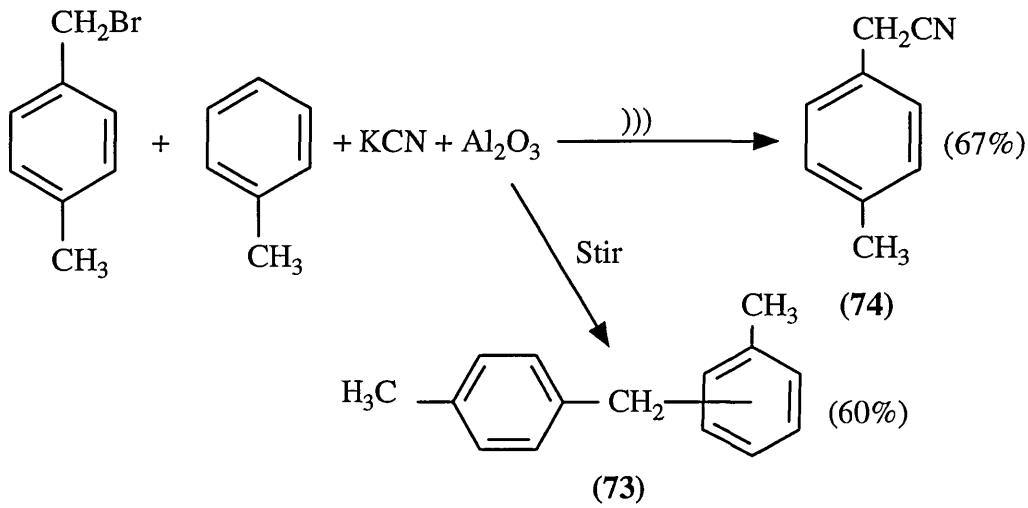


A = 3 x acidic Al_2O_3 - KF, B = 3 x basic Al_2O_3 - KF, C = 3 x basic Al_2O_3 - KF,)))

[Scheme 49]

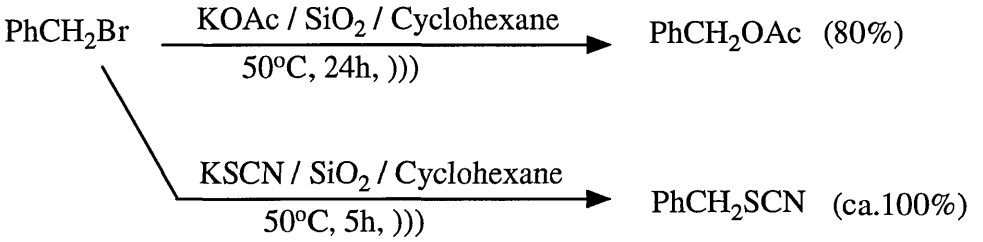
Sonochemical Switching

A now well known phenomenon named as "chemical switching" by Ando[175,176] relates to the Friedel-Crafts reaction outlined below [Scheme 50]. Conventional stirring of the reaction yields the expected Friedel-Crafts product (**73**), which is catalysed by the Lewis acid sites on the alumina surface. However, if the reaction is sonicated the bromine atom in the benzyl bromide is substituted by a cyanide ion. It is proposed that sonication saturates the alumina surface with cyanide ions masking the Lewis acid sites and thus inhibiting the Friedel-Crafts reaction and promoting the substitution reaction to give the product (**74**) [Scheme 50].



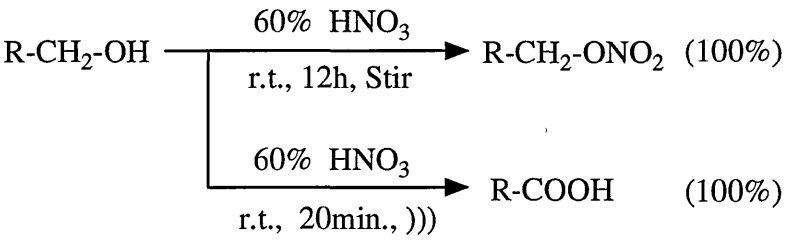
[Scheme 50]

The halogen atom on a benzyl halide has been substituted by an acetate, cyanide or thiocyanate ion by sonicating silica gel with the corresponding salt[177] previously adsorbed onto the surface of the silica [Scheme 51].



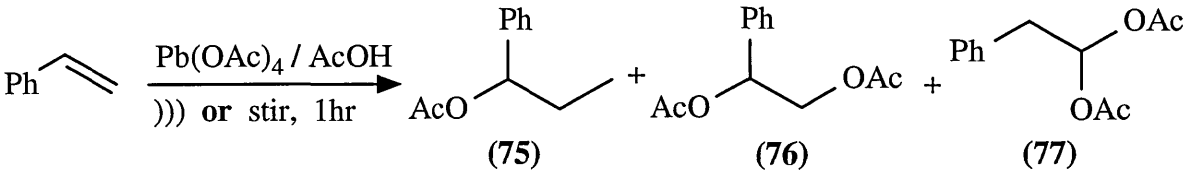
[Scheme 51]

The stirring of an alcohol with nitric acid has been shown to produce an alkyl nitrate in quantitative yield while the same mixture under sonication[178] gives as good a yield of the corresponding carboxylic acid [Scheme 52].



[Scheme 52]

It is appropriate to discuss another example of sonochemical switching at this point. Under various reaction conditions styrene reacts with lead tetra-acetate in acetic acid[179] to give a variety of acetates (**75, 76,** and **77**) [Scheme 53].

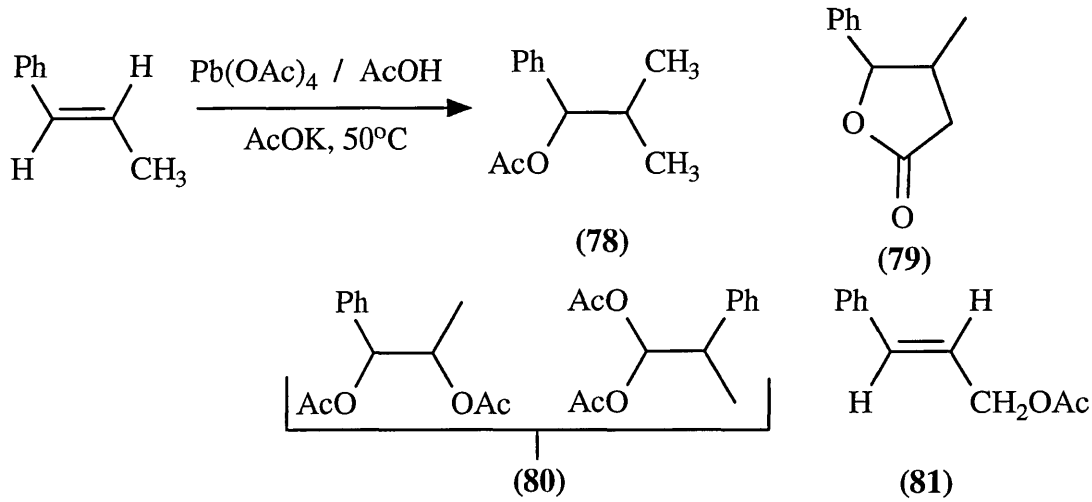


[Scheme 53]

Previous mechanistic studies of the reaction[180,181] have shown that the products obtained depend on whether they have been formed *via* a radical or ionic pathway. Compound (**75**) results from a radical chain reaction, (**77**) from an ionic process and (**76**) is formed by the two concurrent reactions. It was found that only compound (**77**)

was obtained at 50°C or less with mechanical stirring. Above 50°C the radical pathway intervened and **(75)** was the major reaction product at 100°C. Under all temperature conditions (up to 62°C) it was found that the radical pathway product **(75)** was the major product when the reaction was sonicated in a reactor similar to a Suslick cell. However, it was found that indirect sonication with a cup horn required far higher power to obtain any radical reaction. It was also found that the addition of radical scavengers (p-benzoquinone or 4-t-butylcatechol) inhibited the reaction and only a small amount of **(77)** was obtained.

Under similar conditions[182,183] *trans*-β-methylstyrene reacts to give products resulting from radical (**78** and **79**) and ionic (**80** and **81**) processes. It was found that sonochemical switching occurred in a similar manner to that previously shown[179] for styrene. Scheme 54 illustrates how sonication (both direct and cup horn) switched the main reaction pathway from ionic to radical.



		Product Yield			
Conditions	Time / h	**(78)**	**(79)**	**(80)**	**(81)**
Stir	24	0	0	12.5	24.3
)))[a]	1	29.2	34.6	3.9	0.5
)))[b]	1	16.2	14.8	3.2	0

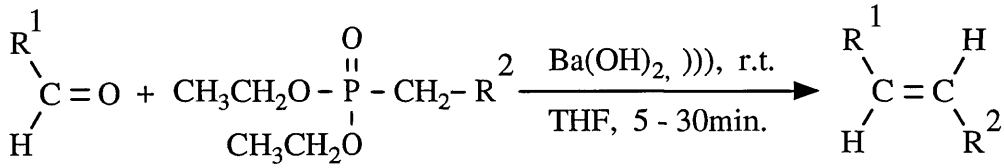
a = Sonochemical reactor at 190W, b = Cup horn at 380W.

[Scheme 54]

The authors explain the results in terms of the "hot spot" theory where the transient higher temperature that results from cavitation has promoted the radical reaction which is a similar effect that occurs when the mechanically stirred reaction is heated to the higher temperatures.

Effect of Ultrasound on a Catalyst Surface - The Wittig-Horner Reaction

To comment more fully on why ultrasound should promote catalytic reactions Luche *et al*[2] cites the work of Sinisterra and co-workers[184-186] as providing an insight into what is actually happening on the surface of the catalyst. It is proposed that ultrasound has a chemical role in the rate and yield acceleration rather than a simple mechanical role of agitation. The Wittig-Horner reaction is used to illustrate the argument. The Wittig-Horner reaction is a method for the synthesis of functionalised olefins such as acrylates or acrylonitriles from aldehydes. Although good yields are obtained the reaction suffers from long reaction times, however, sonication of the reaction reduced the reaction time and improved[186] the yields [Scheme 55].



$R^1 = Ar$ $R^2 = CO_2R^3$ or CN

[Scheme 55]

The reaction is initiated by a single electron transfer (SET) between the starting phosphonate and the basic sites of the catalyst (barium hydroxide). A radical anion is produced which is adsorbed onto the surface of the catalyst. This radical anion then reacts with an ·OH radical that has been produced from the sonolytic cleavage of water. It is this crucial step which causes the difference in the reaction rates between the sonicated and quiet reaction. The hydroxyl radical generated begins a catalytic cycle at the surface of barium hydroxide, where a series of oxidative-reductive electron exchanges occur. The ylide formed reacts with the aldehyde to form the 1,2-oxaphosphetane which is then broken up by water to produce the functionalised olefin, phosphine oxide and a hydroxyl ion. This hydroxyl ion then regenerates the basic site on the catalyst surface by a second SET process giving ·OH that can be reused in the formation of the ylide as can be seen in Scheme 56. Only a catalytic amount of the hydroxyl radical has to be produced for the reaction to be accelerated.

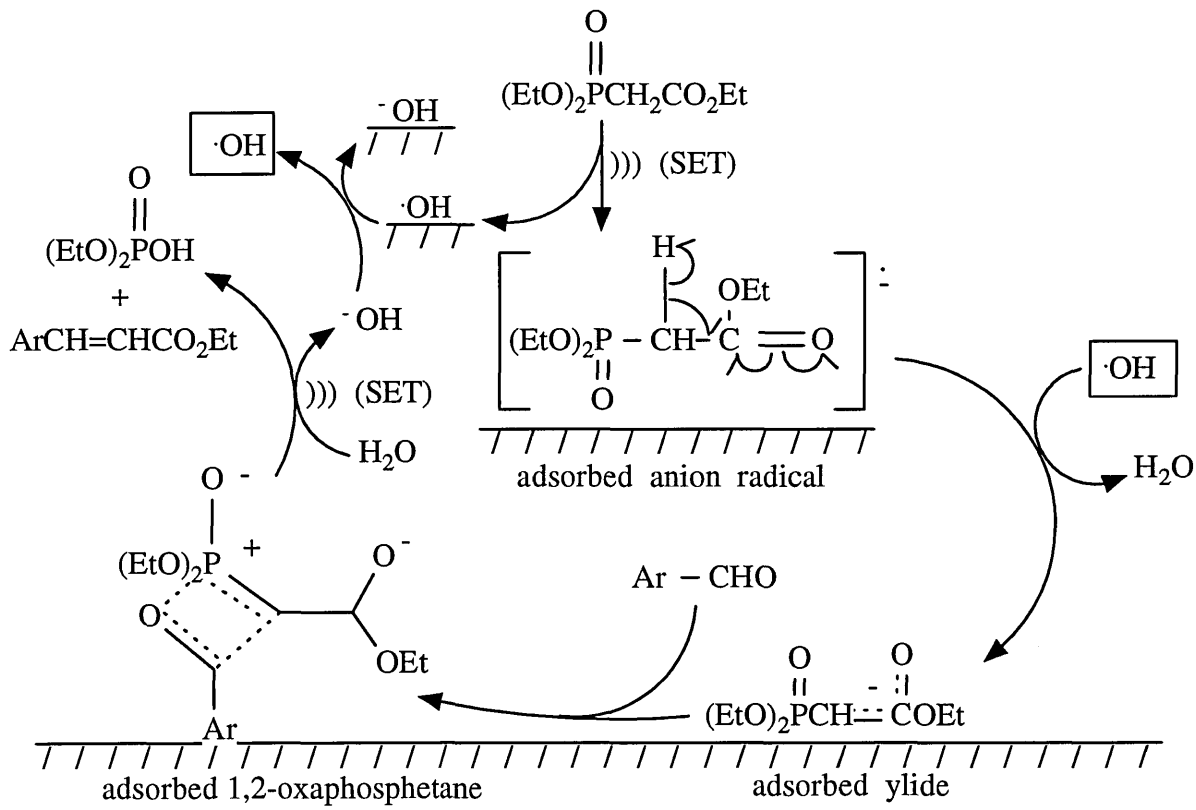
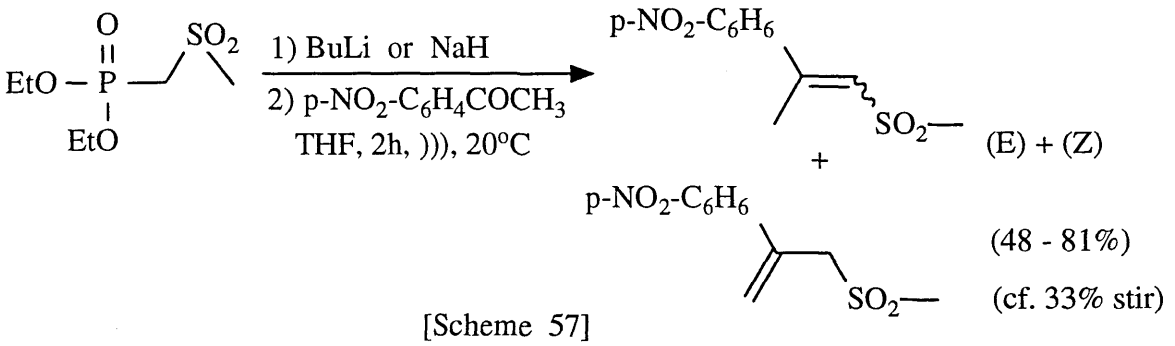


diagram adapted from J.V.Sinisterra, A.Fuentes, J.M.Marinas, *J. Org. Chem.*, **52**, 3875, 1987

[Scheme 56]

A homogeneous Wittig-Horner reaction has also been shown[187] to be sensitive to the effects of ultrasound. Ultrasound substantially improves the Wittig-Horner reaction between the sulfonomethylphosphonate anion and *p*-nitroacetophenone [Scheme 57]. The authors hypothesise that ultrasound promotes a radical mechanism in the reaction and avoids the enolisation, an ionic, ultrasound insensitive process which can give unwanted side products in conventional reactions.



[Scheme 57]

1.3.4 METALLIC CATALYSTS

Hydrogenation

Maltsev has highlighted[188] the effect of ultrasonic activation on heterogeneous catalysts. The activity of palladium, platinum and rhodium blacks were all altered by either preparing the catalyst or reacting it under sonication. Various effects are described including that of frequency which can increase or decrease the rate of reaction, e.g. the hydrogenation of 1-hexene is accelerated when the frequency is increased [Figure 1.15]. Other investigations into the effect of ultrasound on catalysis include the hydrogenation of unsaturated esters in cyclohexane solution[189] in the presence of Raney nickel. The authors conclude that the relative rates of sonochemical reactions compared to quiet reactions depend on two important factors **i)** that an optimal frequency exists and **ii)** that an optimal energy at that frequency produces the highest relative rate. These effects are related to cavitation and its maximisation.

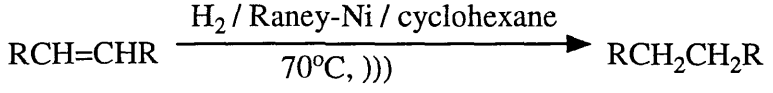
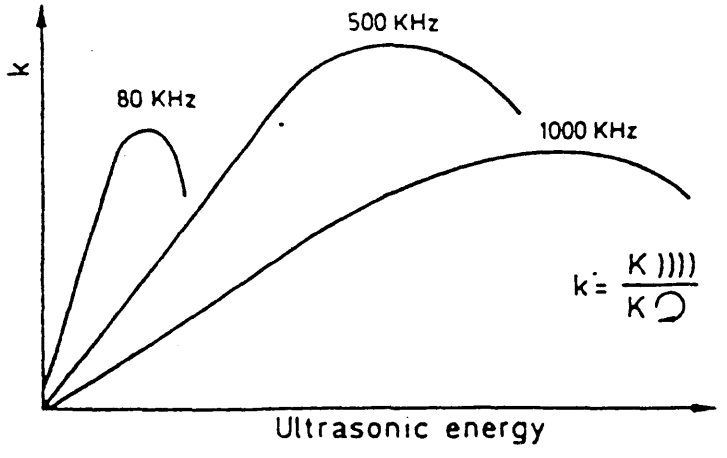
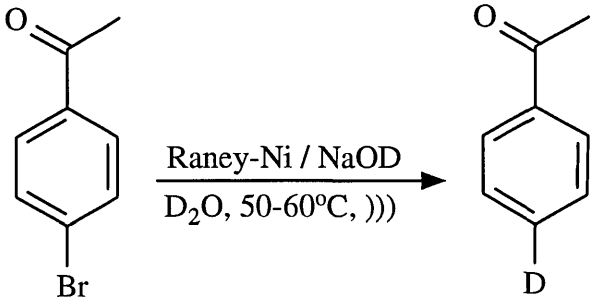


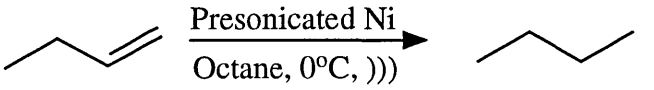
Figure 1.15 Frequency vs. Reaction Rate[189]



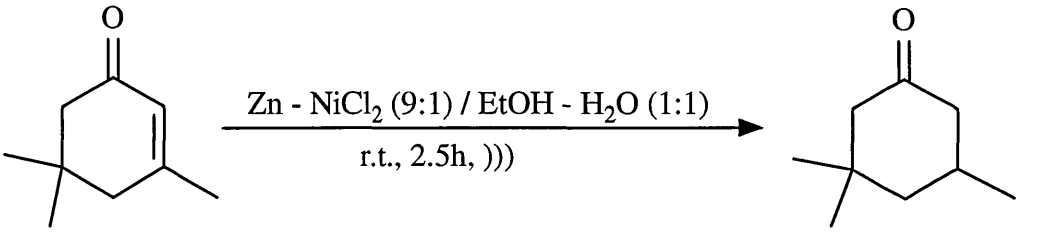
Other hydrogenations have included the hydrogenation of a benzyl ether[190] using a palladium catalyst and the introduction of deuterium into sugar derivatives[191] using Raney nickel. Deuteration of *p*-bromoacetophenone[192] in a silent reaction gave a mixture of the mono-, di-, and tri-deuterated compounds, however the sonicated reaction is highly selective with a good yield.



Nickel powder is usually inactive as a hydrogenation catalyst, however presonication of the powder increases its catalytic activity by a factor of ca.10^5. Alkenes are readily hydrogenated[193] using the resultant catalyst. Ultrasound has activated the surface by removing the passive oxide layer and leaving a freshly exposed metallic surface.

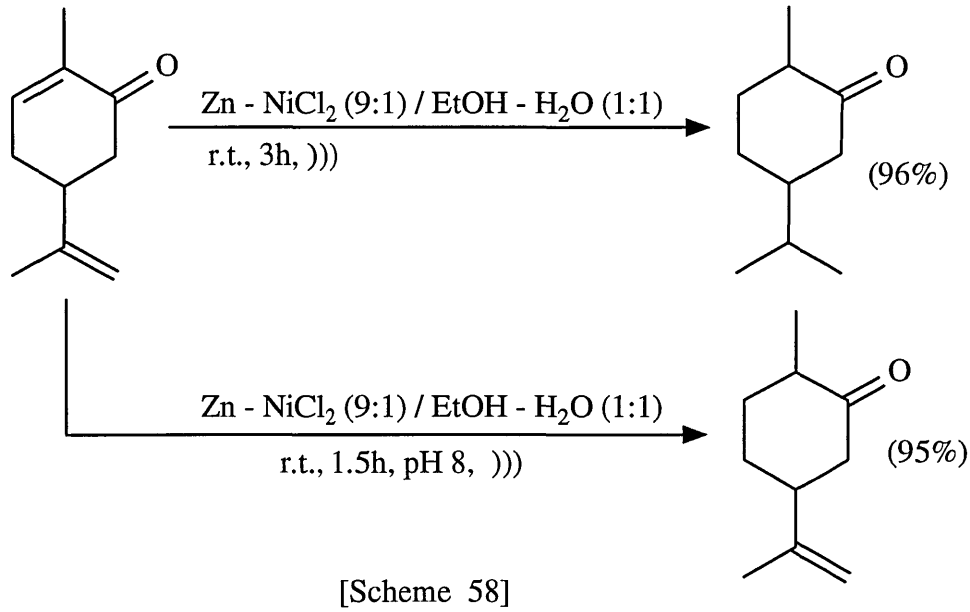


Nickel chloride can be sonochemically reduced with zinc powder to produce catalytically active nickel. Ultrasound also activates the excess zinc[194] which reacts with the water present in the medium to produce hydrogen gas. The system then obtained is one where the catalyst and the reagent are both produced *in situ*. This system has been shown to selectivly reduce the carbon-carbon double bond in α,β-unsaturated carbonyl compounds.



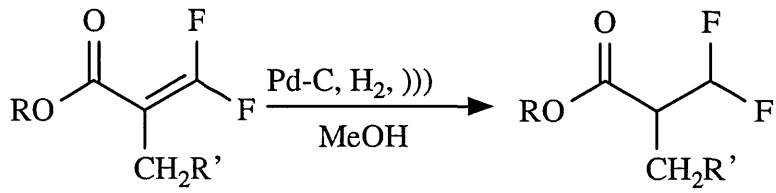
97%
cf. Stir, 48h, 95%.

In this type of reaction selectivity can be altered with pH; for example with carvone when the reaction conditions are kept at pH 8 the unsaturated side group remains unchanged [Scheme 58].



[Scheme 58]

Ultrasound has also been used to effect the hydrogenation[195] of fluorinated acrylic acids and their benzyl esters. This procedure has not been successful with conventional reagents such as sodium borohydride and lithium aluminium hydride. The reaction involves the addition of palladium supported on charcoal (Pd-C) to a methanolic solution of the fluorinated acrylic acid or its benzyl ester, which is then irradiated with ultrasound under a hydrogen atmosphere to yield the α-difluoromethyl carboxylic acid.



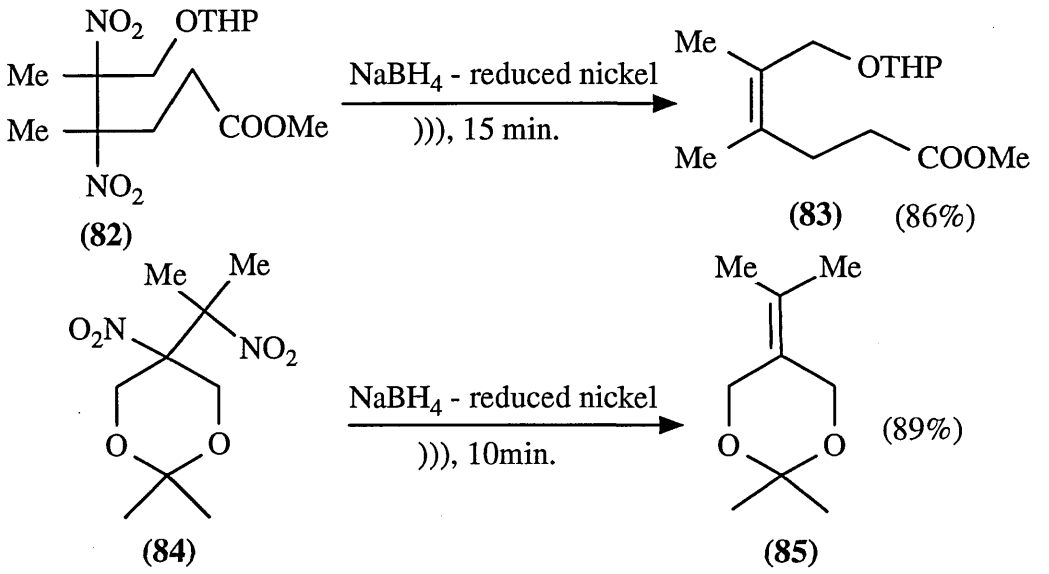
R = H, $PhCH_2$

It was noted that the BINAP-coordinated Ru (II) complex gave enantioselective hydrogenation[196] of the benzyl acrylates (R = $PhCH_2$).

R'	Yield (%)	ee (%)
$-(CH_2)_3CH_3$	78	24
$-(CH_2)_5CH_3$	19	19
$-(CH_2)_7CH_3$	68	31

Oxidation

Tetra substituted functionalised alkenes **(83)** and **(85)** have been prepared from methanolic solutions of functionalised *vic*-dinitroalkanes **(82)** and **(84)** treated with nickel boride ($NaBH_4$-reduced nickel) while irradiated[197] with ultrasound. Ultrasound has provided milder reaction conditions (conventional conditions require Bu_3SnH, benzene, reflux, 10-12hrs) and increased yields. Two examples of the alkenes produced are illustrated below [Scheme 59].

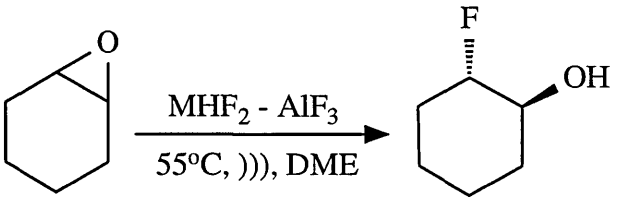


[Scheme 59]

Hydrofluorination

Aliphatic oxiranes have been shown to undergo ring opening to produce fluorohydrins when a combination of aluminium fluoride and alkali metal hydrogen fluoride (MHF_2-AlF_3) is used as a solid reagent[198] under the influence of ultrasound. This is an advance on the more hazardous anhydrous HF which is usually used to introduce fluorine into epoxides.

Cyclohexane oxide is readily converted to trans-2-fluorocyclohexanol under the reaction conditions. Similar yields (50%) can be obtained by stirring but the reaction takes much longer (20hrs) [Scheme 60].



0.5 - 4 hrs, yield 51 - 60%

M = K or Na or NH_4

[Scheme 60]

Even with ultrasound when AlF_3 is not present the reaction does not proceed. When ultrasound is applied with AlF_3 the reaction rate is greatly improved. A mechanism is not proposed but it is believed that MHF_2 and AlF_3 react together to form HF which binds to the surface and reacts immediately to give the fluorohydrin.

1.3.5 REACTIONS WITH METALS

Heterogeneous reactions with metals have been a prime area of research within sonochemistry. This has been due to the effects that cavitation has on metallic surfaces and hence the synthesis of organometallic compounds. The early research in sonochemistry[199] indicated the benefit of ultrasound on the synthesis of organomagnesium, aluminium and lithium compounds.

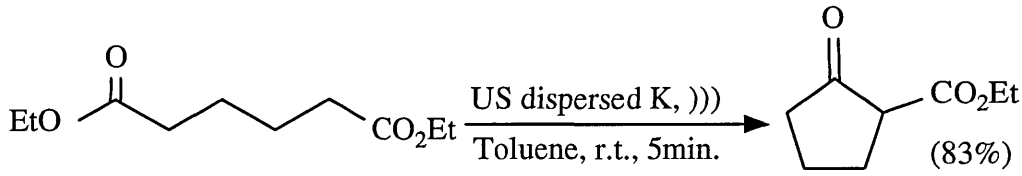
When metals are subjected to cavitation within an ultrasonic field erosion is the major effect[200] which is observed. Erosion rate of the metallic surface increases with a decrease in hardness, illustrated with the erosion rate sequence Cu < Sn < Zn < Mg < Pb. Therefore ultrasound erodes the surface increasing dissolution of the metal and also cleaning off passive coatings such as oxides to expose an active metallic surface which will increase reaction rate and reduce induction times, which is a classic problem of reactions such as the Grignard and Barbier.

Many metals used in organic synthesis cannot be activated by ultrasound because their hardness is to high, or because of strong cohesiveness in passivation layers. However, indirect activation with the reduction of metal halides to active metal powders using ultrasound[201] has been carried out. Conventional methods involve the

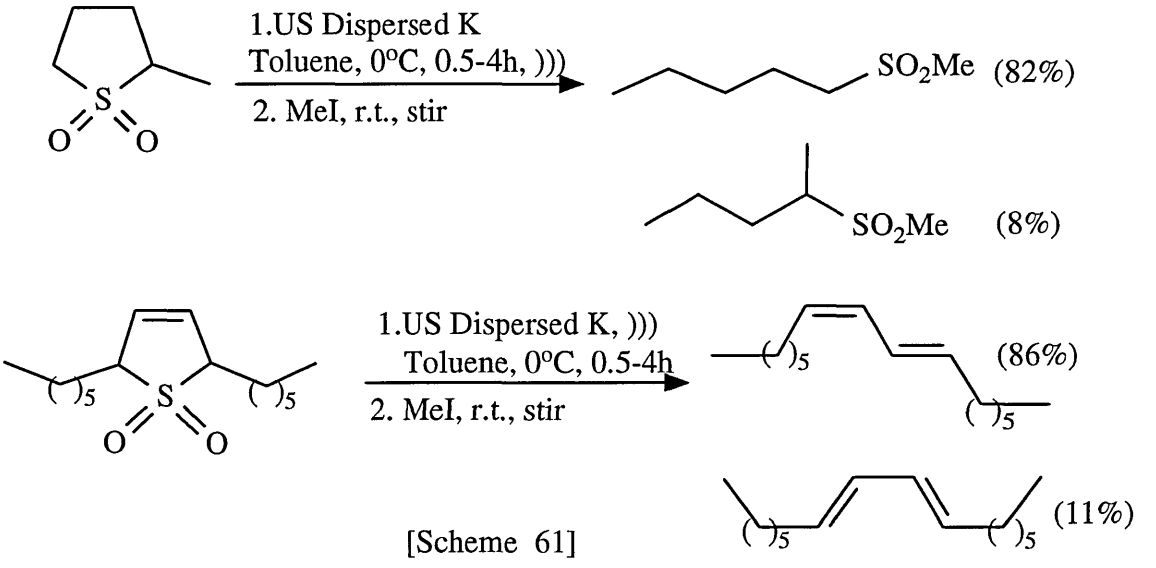
reduction of metal halides with potassium metal in refluxing THF to produce the so-called Rieke powders. The sonochemical method replaces the potassium metal with lithium at room temperature in THF in a cleaning bath. Powders of Zn, Mg, Cr, Ni, Pd, Co and Pb can all be obtained in under 40 minutes compared to 8 hours.

Alkali Metal Reactions

Due to their widespread synthetic use alkali metals have been subjected to a number of reactions under sonochemical conditions. Complexes can be formed at a far higher rate than the equivalent quiet reaction; for example sodium and benzoquinone react to form a complex at a rate 60 fold times higher[202] than the quiet reaction. Aromatic radical anions can be prepared efficiently[203] under various conditions. Anthracene-sodium, biphenyl-sodium, naphthalene-sodium and naphthalene-lithium are all easily prepared in dimethoxyethane or tetrahydrofuran. The induction time is reduced and the solvent can be changed to apolar solvents such as benzene when one equivalent of tetramethylethylenediamine[204,205] is present. The metals are not dispersed under these conditions due to the weak cavitational energy dispersion characteristics of the solvent, and reactions probably occur on the surface of the metal. However, when toluene is used potassium is dispersed into a blue suspension[206], and sodium can be dispersed when xylene is the solvent. The ultrasonically dispersed potassium has been utilised advantageously[206] in the Thorpe-Ziegler and Dieckmann cyclisations, ketone enolisation, and also in the preparation of Wittig-Horner reagents.

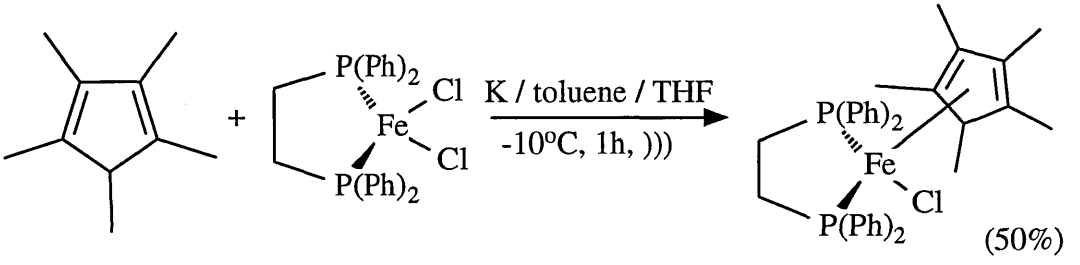


In those reactions mentioned above the US dispersed potassium (UDP) is generally regarded as acting as a base rather than as a single electron transfer agent, with the exception of the reduction of sulphur-carbon bonds in the cyclic sulfone followed by methylation of the intermediate to the resultant open chain sulfones [207] and also the ring opening of 3-sulfolene to the dienes[208] with high stereoselectivity [Scheme 61]. The UDP induced C-S bond cleavage was also found to be enhanced by the slow addition of water in THF[209] or the use of other proton sources[210,211] such as phenol.



[Scheme 61]

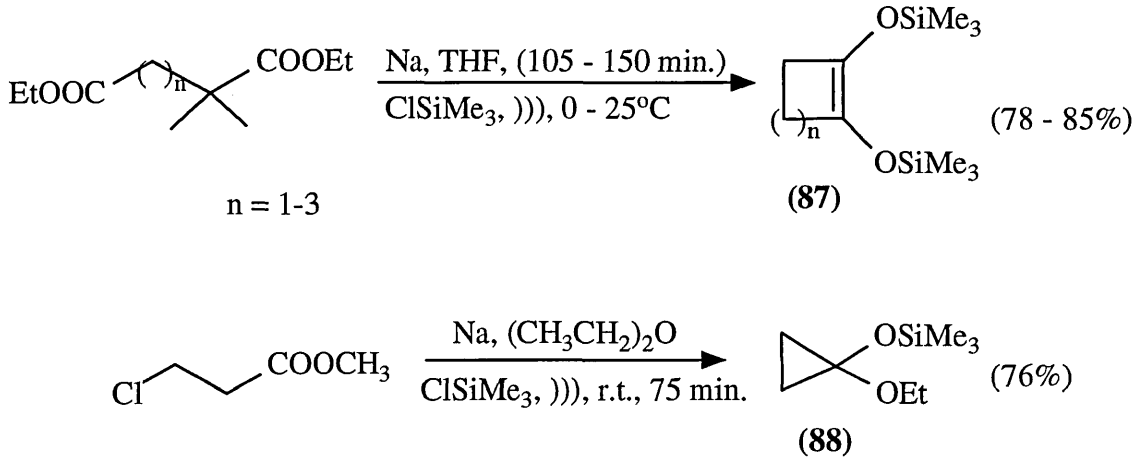
Ultrasonically dispersed potassium can be used in a quite spectacular rate enhancement in the synthesis of cyclopentadienyl iron complex **(86)** below which is prepared in 10 minutes[212] as compared to 7 days using the equivalent quiet synthetic method.



(86)

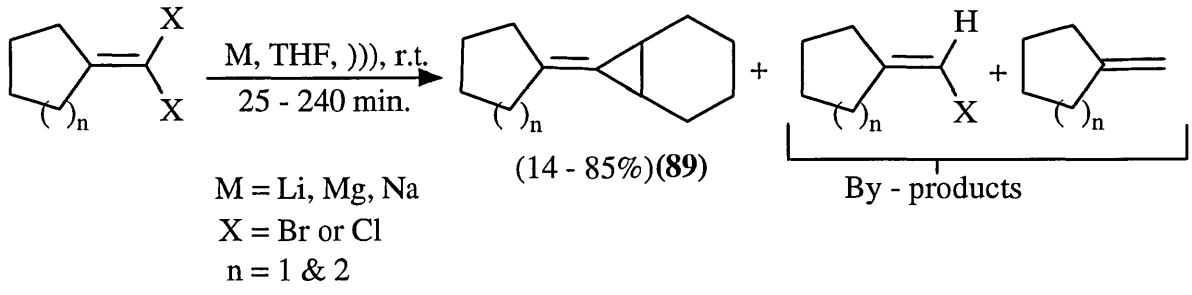
Acyloin coupling, in the presence of chlorotrimethylsilane, of 1,4-, 1,5-, and 1,6-diesters to 4-, 5-, and 6-membered ring products and the cyclisation of β-chloroesters to 3-membered ring products[213], has been simplified and improved by sonochemical activation. For example the cyclisation of diethylsuccinate ester to 1,2-disiloxycyclobutene **(87)** requires refluxing toluene, highly dispersed molten sodium, and freshly distilled $ClSiMe_3$ under nitrogen. Using ultrasound a solution of succinate and technical $ClSiMe_3$ in THF containing metallic sodium cut into small cubic pieces ($5mm^3$) was sonicated at 0 °C or room temperature to give a good yield of the cyclic product within 2 hours. The authors also describe formation of 5- & 6-membered rings under similar conditions.

The cyclisation of several substituted β-chloropropanoates is also described using ultrasound with sodium in ether to the cyclopropane compound **(88)** [Scheme 62].



[Scheme 62]

Lithium, magnesium and sodium have all been used to afford multisubstituted methylenecyclopropanes **(89)** when the metal is sonicated[214] with 1,1-dihaloolefins in the presence of alkenes [Scheme 63].

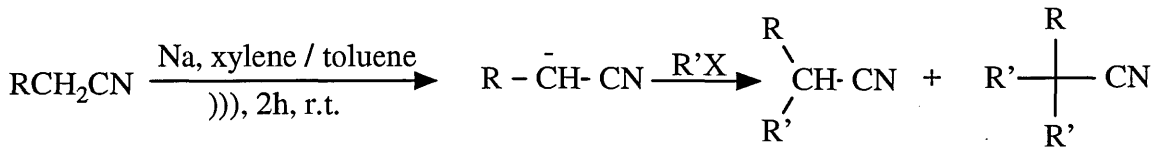


[Scheme 63]

This methylenecyclopropane adduct is difficult to synthesize under conventional methods.

The deprotonation - alkylation of n-alkyl cyanides has been effected by an alkyl halide in a one-pot procedure[215] in the presence of sodium [Scheme 64].

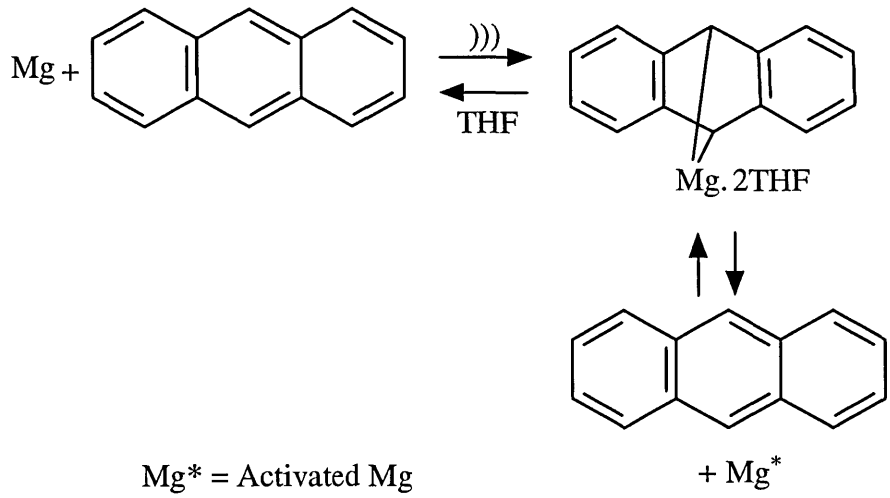
The procedure is more convenient than conventional routes with improved yields obtained. Sonication does not disperse lithium however its surface morphology is modified extensively[2] with ultrasound.



R' = C_3H_7 [Scheme 64]

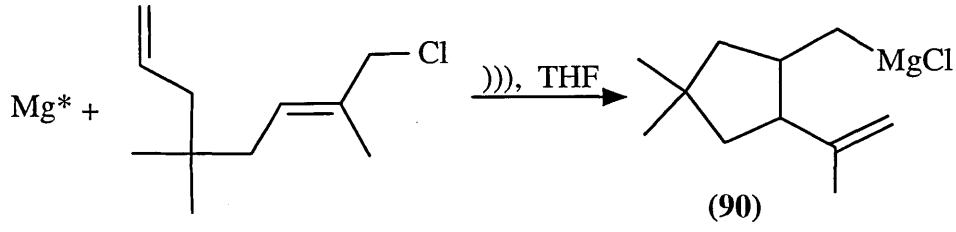
Magnesium & Copper

When magnesium and anthracene are sonicated together in THF a highly active form of the metal is produced[216], which can be utilised in the formation of Grignard reagents [Scheme 65]. The anthracene forms an electron transfer complex with the magnesium, which effectively means the anthracene acts as a phase transfer agent.



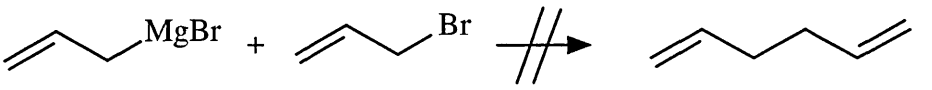
[Scheme 65]

This method can be used to prepare several Grignard reagents from halo-olefins[217] such as the chlorodiene **(90)**.

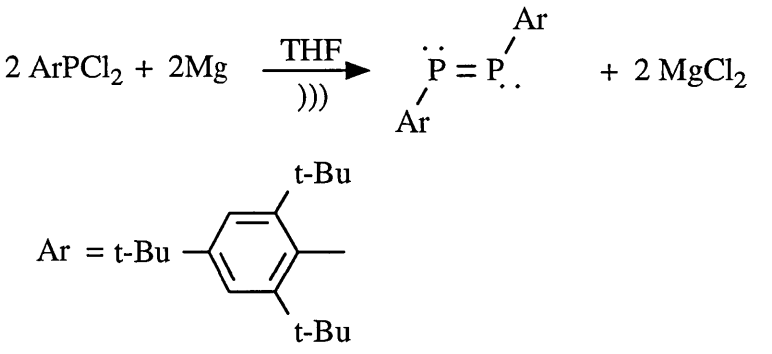


(90)

In the preparation of Grignard reagents from halo-olefins ultrasound reduces side reactions such as the coupling of allyl magnesium halides[218] with the starting halide.



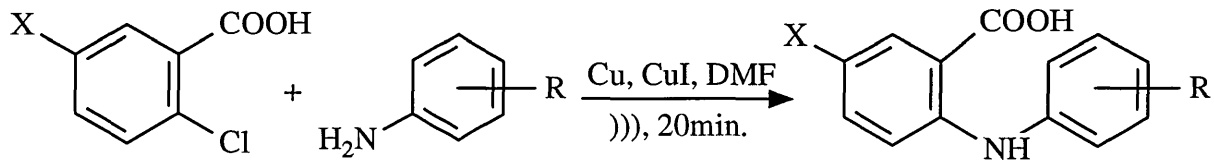
The reaction between magnesium metal and 2,4,6-tri-t-butylphenyldichlorophosphine to form the diphosphine has been accelerated[219] under the influence of ultrasound [Scheme 66]. The yield has been improved (5 °C, 65%) over the quiet reaction (20 °C, 22%) and the yields were found to peak at lower temperatures which agrees[2] with the paradoxal temperature effect.



[Scheme 66]

The authors noted that the same overall yield could be obtained from the silent reaction, and hence reasoned that the ultrasound was having a simple mechanical effect on the reaction, probably due to the depassivation of the magnesium surface.

Ultrasonic irradiation[220] has been shown to improve the synthesis of N-arylanthranilic acids **(91)** through a Ullmann-Goldberg condensation. The reaction of an *o*-halo benzoic acid with aniline in the presence of copper and copper iodide is complete within 20 minutes compared to 4-6 hours for the stirred equivalent [Scheme 67].



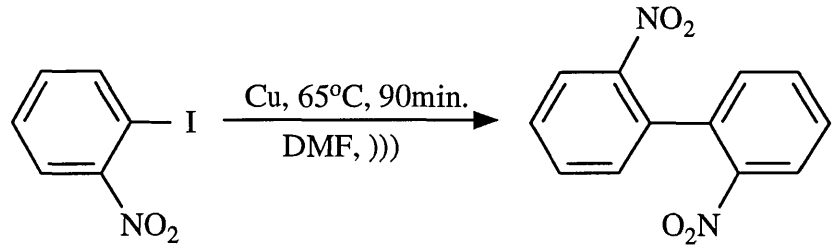
X = H, Cl

(91) (14 - 75%)

R = H, *o-*, *p*-Cl, *o-*, *m*-Me, 2,3-dimethyl, *m*-CF_3, 2-Me-5-NO_2

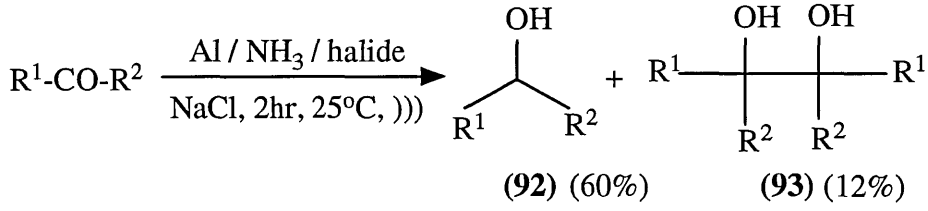
[Scheme 67]

In the Ullmann coupling of halobenzenes, copper has to be reacted with the starting material at high temperatures. The reaction conditions are made much less severe[221] when the copper particle size is reduced by cavitation. The cavitation activates the metallic surface by "scouring" off any oxide passivation that may be present. In this experiment optimisation of copper to halide (4:1) gave an 80% yield in 1.5h, compared to a 5% yield with stirring only.



Aluminium

The reduction of benzophenones and acetophenones to the corresponding monohydric alcohols **(92)** and or the coupled pinacols **(93)** using Al / NH_3 / halide[222] is possible under ultrasonic irradiation.



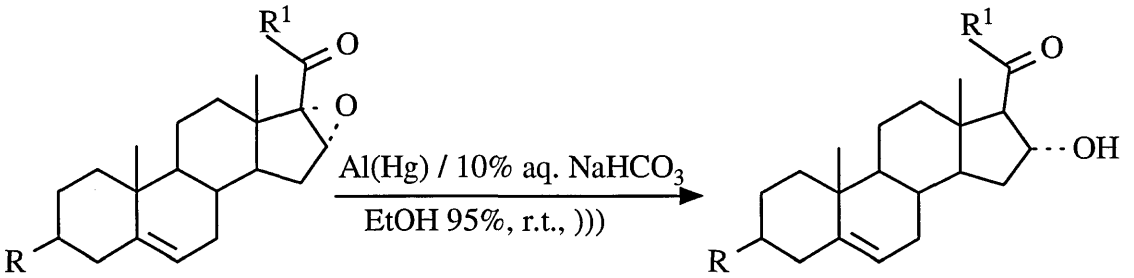
(92) (60%) **(93)** (12%)

Ultrasound reduces reaction time from 24h for conventional stirring to 2h for the sonicated reaction. The addition of sodium chloride is also observed to be an essential component of the reaction i.e. no additive, no reaction. No significant effect on selectivity was observed when NaCl was replaced with LiCl, KBr or $AlCl_3$ but addition of $MgCl_2$ and $ZnCl_2$ resulted in no reaction at all. The addition of iodine

gave a similar result to NaCl etc, but when NH_4Cl was added selectivity became exclusive towards the monohydric alcohol. Methylamine and ethylenediamine were also used as solvents but were less favourable than ammonia.

Several other substituted (chloro, methyl, & acetyl groups) benzophenones were subjected to these conditions and were successfully reduced with various selectivities towards the coupled product. Interestingly, when NH_4Cl was used as the additive the benzhydrols were produced exclusively in good yield (85-98%) which compares directly to the reduction of benzophenone. However the selectivity is reversed towards the exclusive production of pinacols when acetophenones are used as the starting material with NaCl as the additive. When NH_4Cl is added to this reaction a mixture of the pinacols and monohydric alcohols are produced. These changes in selectivity are thought to be due to the stability of the intermediate. Using p-chlorobenzaldehyde as the starting material resulted in no reaction at all, which may have selectivity applications. The addition of DPPH results in inhibition of the reaction which suggests the reaction proceeds through an intermediate anion radical.

The reductive opening of steroidal α-β-epoxy ketones **(94)** and their α-oxygenated (-OH or -Ac) derivatives by aluminium amalgam under ultrasonic irradiation[223] has improved the yields of the respective β-hydroxy ketones **(95)**, minimised by-products, and allowed shorter reaction times (20min - 6hr, cf. 28 - 32hrs) [Scheme 68]. In this study ultrasonic intensity was optimised (100 W cm^{-2}) as was temperature (40 °C). The 21-oxygenated epoxy ketones were found to react much faster than their nonfunctionalised counterparts.



(94) **(95)**

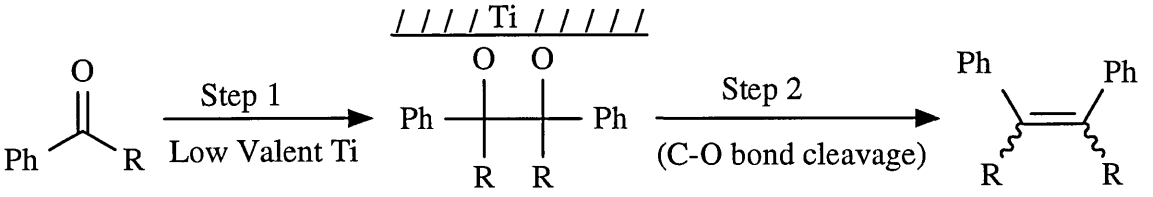
R = OH, OAc

R^1 = Me, CH_2OH, CH_2OAc

[Scheme 68]

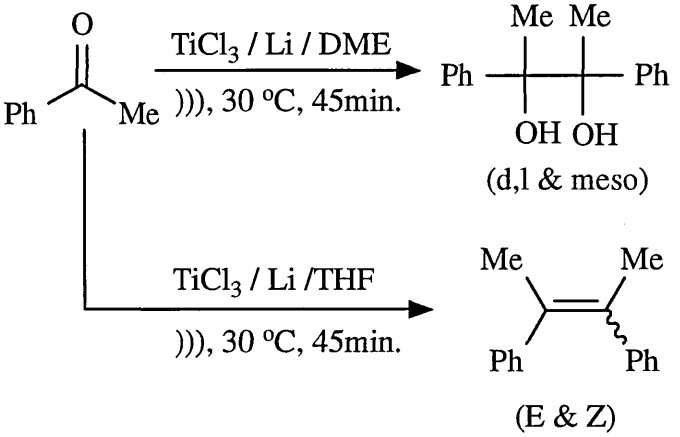
Titanium

Using a combination of ultrasound[224] and appropriate solvent hydrodimerisation (in DME) or reductive deoxygenation (in THF) of carbonyl compounds can be carried out at room temperature within 45-60 minutes. The stereochemistry of the products was found to be dependent on the solvent used when the reaction mixture was sonicated. Under conventional conditions the formation of 2,3-diphenyl-2-butene (83:9, E:Z ratio) is formed from acetophenone in dimethoxyethane in the presence of $TiCl_3$/Li at reflux (16hrs). In this reaction low-valent titanium is generated *in situ* from the $TiCl_3$ and Li, ultrasound accelerates this preparation and allows it to occur at ambient temperature (30°C) in one hour (21:66, E:Z ratio) [Scheme 69].



[Scheme 69]

It was found that by changing the solvent in the refluxed reaction from DME to THF altered the E:Z ratio (25:64) of the alkene, THF was shown to favour the Z-isomer. Pinacols were also produced (25%) when the reaction was stirred at low temperature. When the reaction was sonicated at low temperature in DME pinacols were produced exclusively in a higher yield (75%) [Scheme 70]. Therefore at room temperature sonication of this reaction produces exclusively alkenes in THF or pinacols when the solvent is DME.

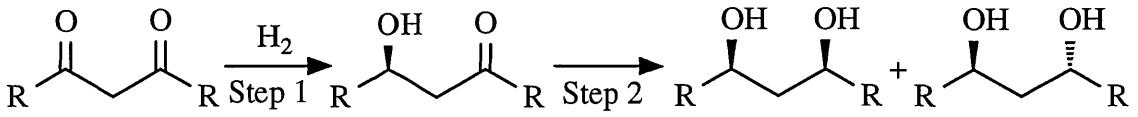


[Scheme 70]

Ultrasound in THF accelerates the deoxygenation by facilitating the cleavage of two carbon-oxygen bonds of the titanium pinacolates resulting in the formation of alkenes.

Nickel

Pre-treatment of a modified Raney nickel catalyst (MRNi) with ultrasound[225] has resulted in an improved catalyst (MRNi-U) which increases hydrogenation rate and stereoselectivity of the catalyst. In an attempt to improve Raney nickel as a enantio-differentiating catalyst conventional chemical methods have involved soaking the Raney nickel catalyst (RNi) in tartaric acid (TA) and NaBr (TA-NaBr-MRNi). This is based on the concept that non-enantio-differentiating (n.e.d.) sites on the catalyst are chemically sensitive and will be dissolved by acid corrosion and the rest can be deactivated by poisoning with the adsorbed NaBr. This increases the ratio of enantio-differentiating (e.d.) sites which will give optically active products. However the hydrogenation rate and durability are not satisfactory in the reaction of 1,3-diketones such as pentane-2,4-dione and 2,6-dimethylheptane-3,5-dione. The pre-treatment of the catalyst with ultrasound was expected to break off the disordered nickel n.e.d. sites which are more fragile than the crystalline e.d. sites. The treatment was also expected to increase finely pulverised pure nickel domains and enhance the hydrogenating activity of the resultant catalyst (TA-NaBr-MRNi-U). It was found that the hydrogenating activity TA-NaBr-MRNi-U was 5 to 10 times higher than the conventional TA-NaBr-MRNi-U. The catalytic activity was also altered with increased enantiomeric excess in the reaction mixture leading to a significantly greater isolated yield of the optical isomer. It was also found that the catalyst was efficient in the hydrogenation of a series of 3-oxoalkanoic acid esters [Scheme 71].

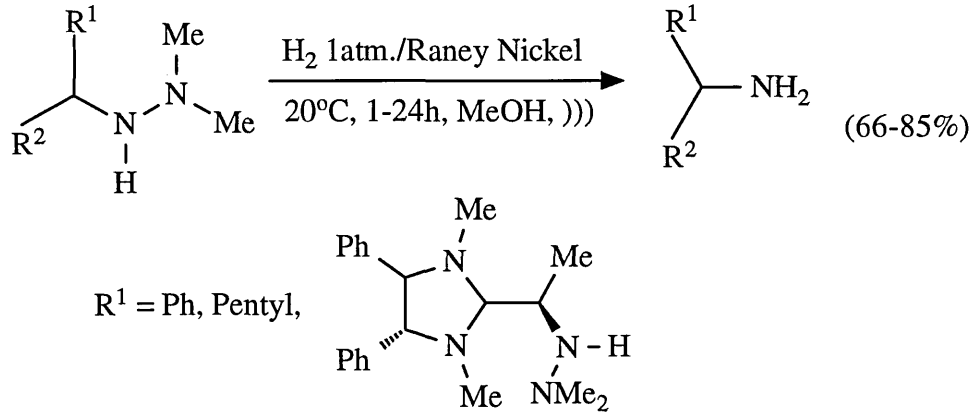


I II III (meso) (R^*, S^*) IV (R^*,R^*)

		Conditions		Prod. ratio			
Substrate	Catalyst	T(°C)	hrs	I:II:III:IV	e.e. of IV	Yield/%	Config.
R = Me	MRNi	100	24	0:20:10:70	90	21	(2R,4R)
	MRNi-U	100	4	0:7:7:86	91	60	(2R,4R)
R = $(Me)_2CH$	MRNi	100	192	1:17:16:66	85	32	(3S,5S)
	MRNi-U	100	60	0:6:22:72	90	59	(3S,5S)

[Scheme 71]

The reductive N-N cleavage on N-substituted N',N'-dimethylhydrazines to give primary amines by Raney nickel/ hydrogen is normally performed at 30-50 °C under 3-50 atm. of hydrogen for 12-24 hours. For more hindered (R=i-Bu or t-Bu) or sensitive (R=Ph) compounds the reaction is sluggish or does not proceed at all with extensive racemisation and decomposition occurring. With ultrasound, supplied from a simple ultrasonic bath, the reaction[226] is performed under atmospheric pressure of hydrogen at room temperature with reaction times as low as one hour [Scheme 72]. The authors observe that no racemisation or debenzylation occurs and the aromatic rings are not hydrogenated. The improvement with ultrasound is assigned to mechanical effects on the nickel particles.



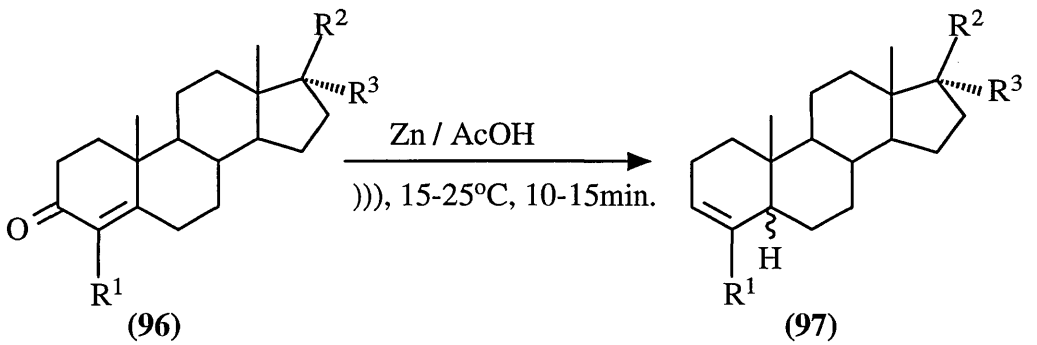
R^2 = Me, i-Bu, t-Bu, Ph, Bu, Pentyl.

[Scheme 72]

It has been found[227] that activated nickel that has been prepared by lithium reduction of nickel iodide under sonication, will efficiently catalyse the hydrosilylation of hexene, styrene, vinyl butyl ether and acrylonitrile under mild conditions. Hydrosilylation catalysts are normally homogeneous platinum and rhodium complexes which are expensive and non-recoverable, whereas the activated nickel is cheap and can be re-used several times.

Zinc

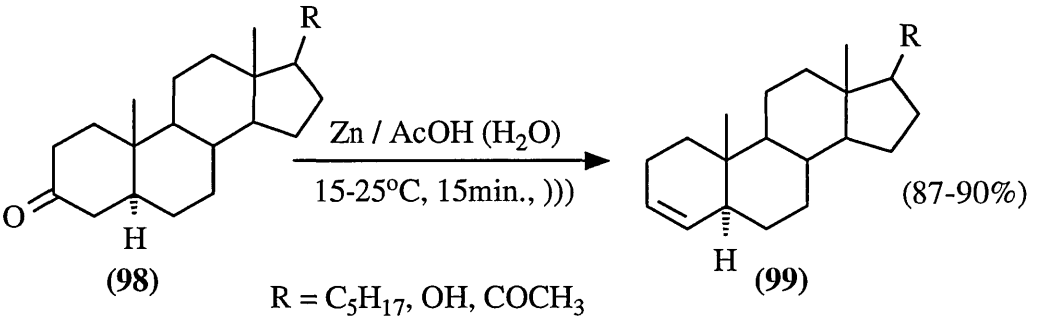
Reduction of α-β-unsaturated ketones with zinc in acetic acid has been significantly improved under sonochemical[228] conditions. Steroids with the 4-en-3-one **(96)** system were reduced to Δ^3-steroids **(97)** [Scheme 73].



[Scheme 73]

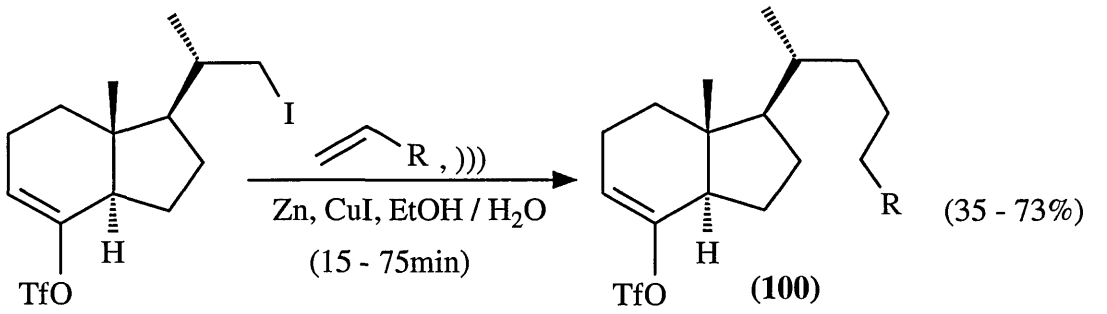
Almost quantitative yields were obtained in a short time (15mins cf. 1-5hrs for silent reaction) with variable ratios of the epimeric mixtures. The activation of metal powder in heterogeneous solid-liquid systems is well established[229] in the literature.

A Clemmensen-type reduction of carbonyls **(98)** to methylene groups **(99)** in steroids has been reported where deoxygenation of 3-oxosteroids with unactivated commercially available zinc dust in acetic acid or acetic acid/water was achieved in 15 minutes at room temperature[230] [Scheme 74] with sonication.



[Scheme 74]

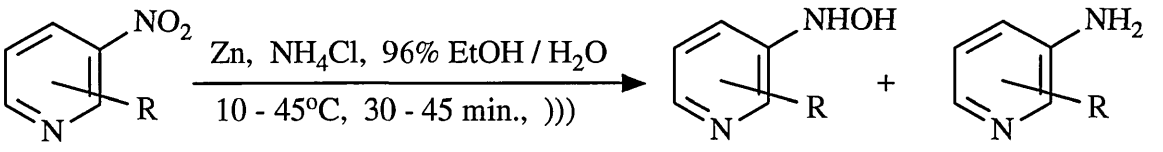
In the preparation of vitamin D_3 the preparation of the intermediate **(100)** was found to benefit[231] from the application of ultrasound. Sonication of the iodotriflate with zinc, CuI in EtOH / H_2O and methyl acrylate afforded the ester in good yield (65%). This reaction does not proceed under stirring alone. With the purpose of applying this synthesis to a wider range of side chain analogs other olefins were studied [Scheme 75]. The reaction is thought to proceed under a sonochemically promoted single electron transfer from the metal to the C-X bond.



R = CO_2CH_3, $COCH_3$, CN, $CONH_2$, SO_2CH_3, SOPh

[Scheme 75]

The sonochemical synthesis[232] of vicinally substituted N-(3-pyridyl)hydroxylamines from the reduction of the corresponding nitropyridines with $Zn/NH_4Cl/EtOH$ has been found to be an improvement over the mechanically stirred equivalent [Scheme 76]. The selectivity towards the production of the hydroxylamine over the amine was found to be moderately improved. This, the authors postulate is due to ultrasound preventing the hydroxylamine from being adsorbed onto the metal surface and thus preventing the over reduction to the amine.



R = 2-Cl, 2-MeO, 2-Cl-5-Me, 4-MeO, 4-EtO (75 -98%)

[Scheme 76]

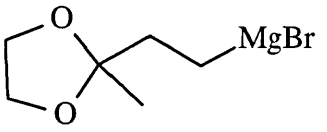
1.3.6 ORGANOMETALLIC SINGLE ELECTRON TRANSFER TYPE REACTIONS

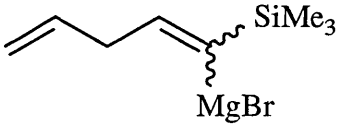
Single electron transfer is the primary process that is accepted to occur[233] in the preparation of organometallic compounds from organic halides. The following reactions can all be included under this heading.

Lithium & Magnesium with Organic Halides

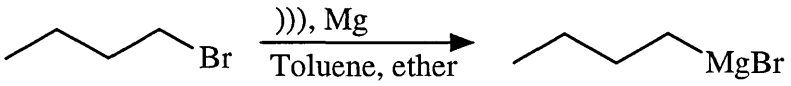
As early as 1950[199] the formation of organolithium and organomagnesium reagents in moist diethyl ether was reported. Later, several alkyllithium reagents were prepared[234] with improved initiation and reaction rates but no improvement in overall yield. Organomagnesium derivatives were also prepared[235] with the same

observations of rate, initiation and yield. These reactions all displayed the possibility of being able to utilise damp solvents, compared to the rigorous drying procedures required under conventional conditions. Lithium has since been used to prepare isopropyllithium under sonication[236], as has magnesium to prepare the functionalised Grignard reagents[237,238] illustrated below, a cyclic ether and allylic trimethylsilyl compounds.

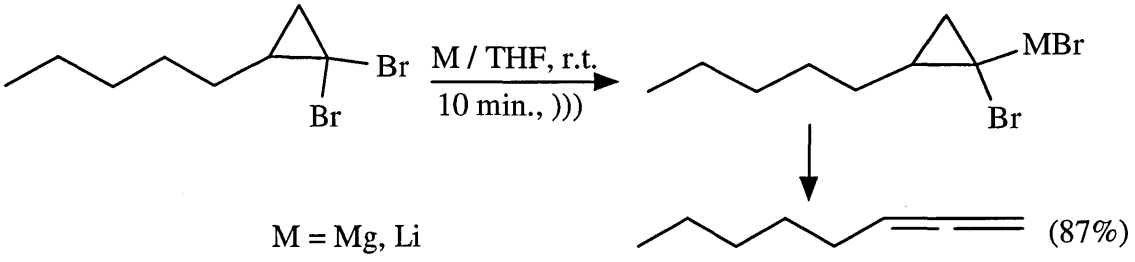




As discussed earlier in Section 1.3.5 the preparation of Grignard reagents are accelerated when irradiated with ultrasound, butyl magnesium bromide, for example, is prepared in toluene in the presence of small quantities of diethyl ether.



When geminal dihalocyclopropanes are sonicated[239] directly with magnesium or lithium in THF at room temperature the α-halolithio- or magnesio compounds are generated [Scheme 77]. This reaction usually undergoes a halogen-metal exchange with an auxiliary organometallic.

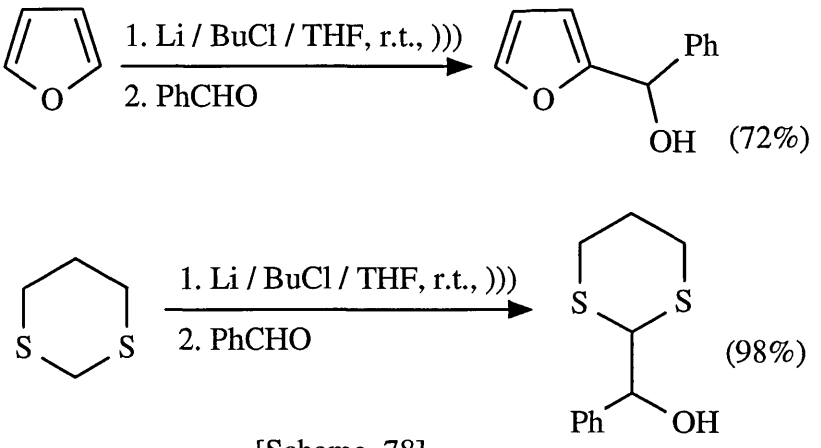


[Scheme 77]

Lithium Exchange with Hydrogen

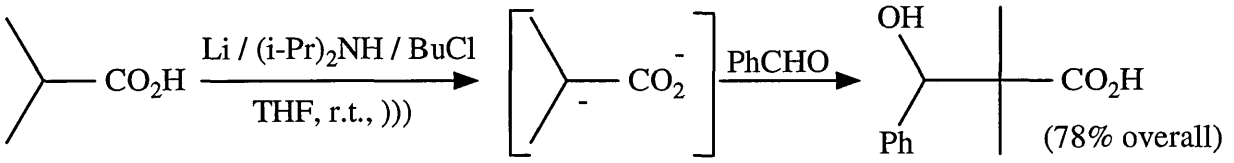
Primary, secondary or tertiary butyllithium is used frequently to prepare organolithium compounds by hydrogen-metal exchange. These reagents can be prepared using sonication[240] and *in situ* reaction can be carried out successfully with a variety of substrates. The reagent lithium diisopropylamide can be prepared directly (92%) from diisopropylamine in a short time in THF which is the solvent required for further use.

This synthetic method can then be used to prepare several compounds from various substrates, two of which are listed below [Scheme 78].



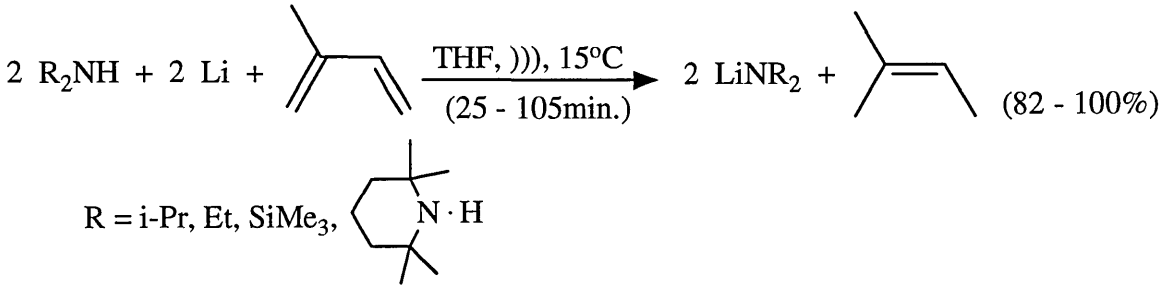
[Scheme 78]

It has also been shown that the discrete preparation of lithium diisopropylamide may be unnecessary, with the example shown of the generation of the isobutyric acid dianion [Scheme 79].



[Scheme 79]

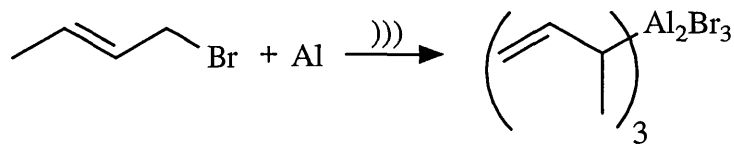
A cheap and simple method for the preparation of lithium salts of hindered secondary amines by ultrasonic irradiation[241] of lithium and the amine substrate in THF in the presence of an electron carrier (isoprene) has been reported [Scheme 80]. Isoprene is chosen as the electron carrier because of its easy manipulation.



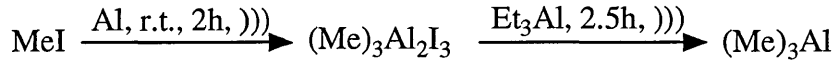
[Scheme 80]

Aluminium, Zinc, Palladium, & Boron with Organic Halides

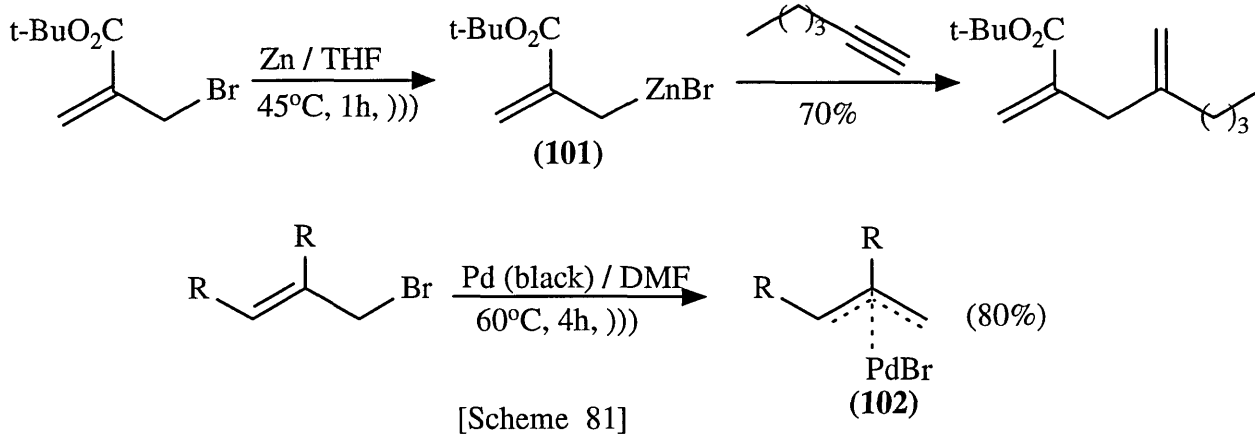
Organoaluminium compounds have been successfully prepared sonochemically[242] and the conditions required are much milder and quicker than the alternative quiet conditions. For example the synthesis of tris(1-methyl-2-butenyl)dialuminium tribromide has been successfully carried out.



Sonication at room temperature of methyl iodide with aluminium for 3 hours gave an excellent yield (96%) of trimethyldialuminium tri-iodide[243] compared to the silent process which after 2 hours stirring at room temperature gave no product. The product can be sonicated with triethylaluminium for 2.5 hours at room temperature to form trimethylaluminium, whereas 100 °C and 6.5h are required to obtain the same yield by a silent reaction.



A direct sonochemical reaction from the metal can also be used to prepare allylic derivatives of zinc **(101)**[244] and palladium **(102)**[245] [Scheme 81].



[Scheme 81]

The preparation of arylzinc compounds which contain electron withdrawing groups at the ortho position is sonochemically[246] enhanced. The reaction of aryl iodides with zinc powder in TMU (tetramethylurea) without ultrasonic irradiation gives a similar yield but over a longer time period [Scheme 82]. Substitution at the meta or para

position was found to reduce yields. The author then successfully cross coupled the arylzinc compound with aryl halides using palladium(0) catalyst to afford asymmetrical and multifunctional biaryls in good yields.

$$R\text{-}C_6H_4\text{-}I \xrightarrow[\text{))), Zn, 30°C}]{\text{TMU, (5-20h)}} R\text{-}C_6H_4\text{-}ZnI \ (38\text{-}96\%) \xrightarrow[\text{Pd(0)}]{R^1\text{-}C_6H_4\text{-}X} R\text{-}C_6H_4\text{-}C_6H_4\text{-}R^1$$

$R = o\text{-}CO_2CH_3,\ o\text{-}CON(CH_3)_2,\ o\text{-}CN,\ o\text{-}Cl,\ o\text{-}CF_3,\ o\text{-}Br,\ o\text{-}COCH_3$

[Scheme 82]

To synthesise organoboranes a transmetalation process is required. To prepare trialkyl boranes in high yield a Grignard reagent has to be formed first which is followed by an *in situ* transmetalation[247] with boron trifluoride etherate [Scheme 83].

$$3\ RX \xrightarrow[\text{r.t., 15 - 30min.,)))}]{BF_3.Et_2O\ /\ Mg\ /\ Et_2O} R_3B \ (44 - 100\%)$$

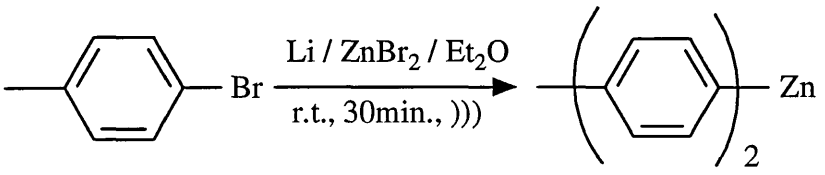
$R = Pr,\ Ph,\ PhCH_2,\ Allyl$

[Scheme 83]

The ultrasound assisted preparation of triethylborane is simply carried out by sonicating[248] bromoethane with aluminium and triethylborate. The straightforward synthesis of these boron compounds using ultrasound is surprising considering that the solvents used liberate a very weak cavitation energy, due to their volatility cushioning the cavitation (solvent effect).

$$3\ EtBr \xrightarrow[\text{2. } B(OEt)_3]{\text{1. Al, 10-20 min.,)))}} Et_3B \ (90\%)$$

Transmetalation is also used to prepare organozinc compounds. These are obtained in high yields utilising an organic halide and lithium (also magnesium) to give the corresponding reagent, which then reacts instantaneously through a metal exchange *in situ* with the zinc bromide[249], but when dialkyl compounds are used as the substrate a sonic probe is required[250]; the reason for this difference is not explained.



Organometallic Wurtz Coupling

Ultrasound can have a profound effect on Wurtz-type coupling in organometallic chemistry. For example, the coupling of organic halides, RX, where R= aryl, benzyl[251], benzoyl and alkyl is generally complete within 12 hours with moderate yields. Without ultrasound little or no reaction occurs [Scheme 84].

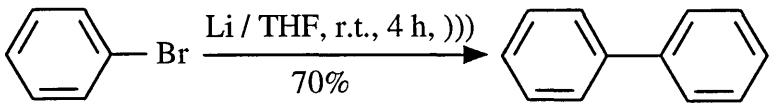
$$\text{R-X} \xrightarrow[)))\text{, 10 - 40hrs}]{\text{Li / THF}} \text{R-R} \quad (36 - 73\%)$$

R = aryl, benzyl, benzoyl, alkyl

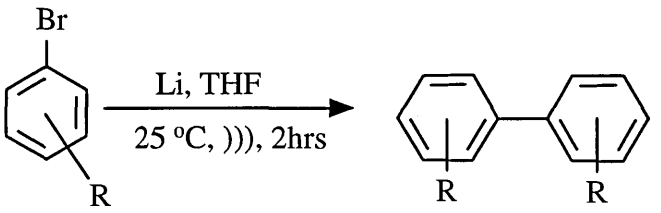
X = Cl, Br, I

[Scheme 84]

When bromobenzene is sonicated with lithium in THF the biphenyl is formed[252] in within 4 hours.



The Wurtz-type coupling with ultrasound has also been examined[253] using 2-bromopyridine as substrate. The dimer products were 2,2'-bipyridine, 4,4'-bipyridine, and 2,4'-bipyridine which is significantly different from the silent reaction which produces dimers that are bonded at the positions previously occupied by the halogen atom. Any crossed products in the silent reaction occur in yields less than 1%. The authors suggest that the unexpected yield of 5% of the crossed 2,4'-bipyridine in the ultrasound reaction may be due to the ultrasound augmenting the radical mechanism at the metal surface. The mechanism of this reaction has been investigated further[254] by studying the products obtained when substituted bromobenzenes are used as substrates, and what effect radical scavengers have on this reaction [Scheme 85].



Product Distribution

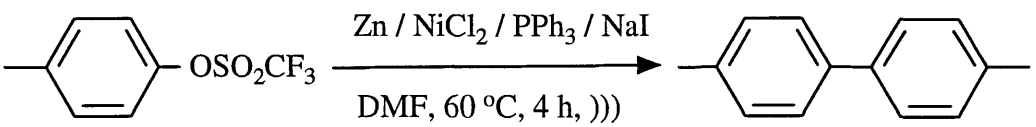
R	Product (% yield)		
H	biphenyl (80)		
2-Me	2,2'-bitolyl (16)	2,3'-bitolyl (17)	2,4'-bitolyl (5)
3-Me	2,3'-bitolyl (6)	3,3'-bitolyl (61)	3,4'-bitolyl (19)
4-Me	2,4'-bitolyl (2)	3,4'-bitolyl (25)	4,4'-bitolyl (52)

Stir equiv. yield < 9%

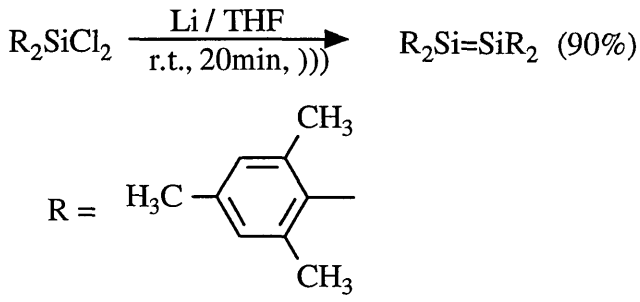
[Scheme 85]

The number of mixed bitolyls from this reaction suggest a mechanism involving one or more radical intermediates. Therefore the authors repeated the coupling of bromobenzene under air and oxygen which reduced the yield considerably (65% and 20% respectively). Considering the radical inhibiting effect of oxygen the authors reasoned that radicals were responsible for the reaction mechanism. The addition of radical scavengers 3,3,5,5-tetramethylpiperidine-N-oxide, (TEMPO), or 2,2'-diphenyl-1-picryl hydrazyl (DPPH) all inhibited the reaction. Therefore, radical intermediates were shown to occur in the sonochemical coupling of bromoaryls.

The coupling of aryl compounds is made more effective by reacting[255] an aryl trifluoromethane sulfonate with zinc powder and a low valent nickel compound.



Chlorosilanes can also be effectively coupled using lithium with sonication[256], for example tetramesityldisilene is prepared from dichlorodimesitylsilane in good yield [Scheme 86].

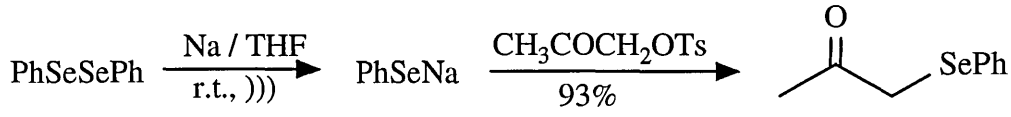


[Scheme 86]

Less hindered dichlorosilanes have been converted into polysilanes[257], which have a higher molecular weight when prepared under sonication. In this case the solvent used was toluene and the metal was sodium.

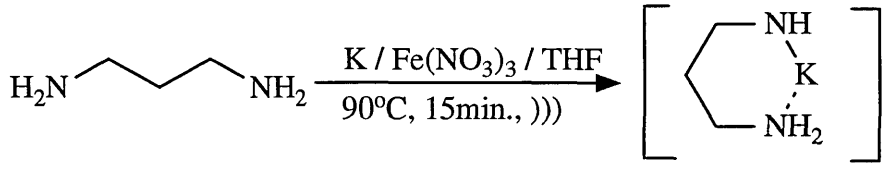
Heteroatom Organometallics

When diphenyldiselenide is sonicated with lithium in THF it is cleaved to form the insoluble reagent sodium phenylselenide as a colloidal suspension. This reagent can then be reacted[258] with various substrates such as tosylates, epoxides and halides [Scheme 87].

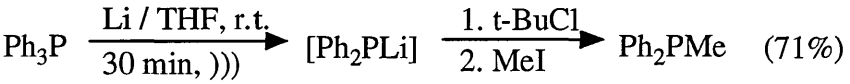


[Scheme 87]

Potassium 3-aminopropylamide can be prepared *via* hydrogen-metal exchange by sonicating[259] the diamine and potassium metal in THF containing a trace of ferric nitrate.

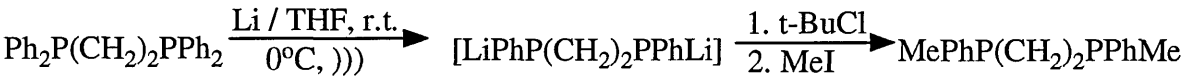


Diorganophosphide anions can be easily prepared from phosphine substrates. These anions can then be used to prepare various monophosphines and diphosphines. The cleavage of the phosphorus-phenyl bond is carried out[260] using lithium in THF, and is accelerated by ultrasound [Scheme 88].



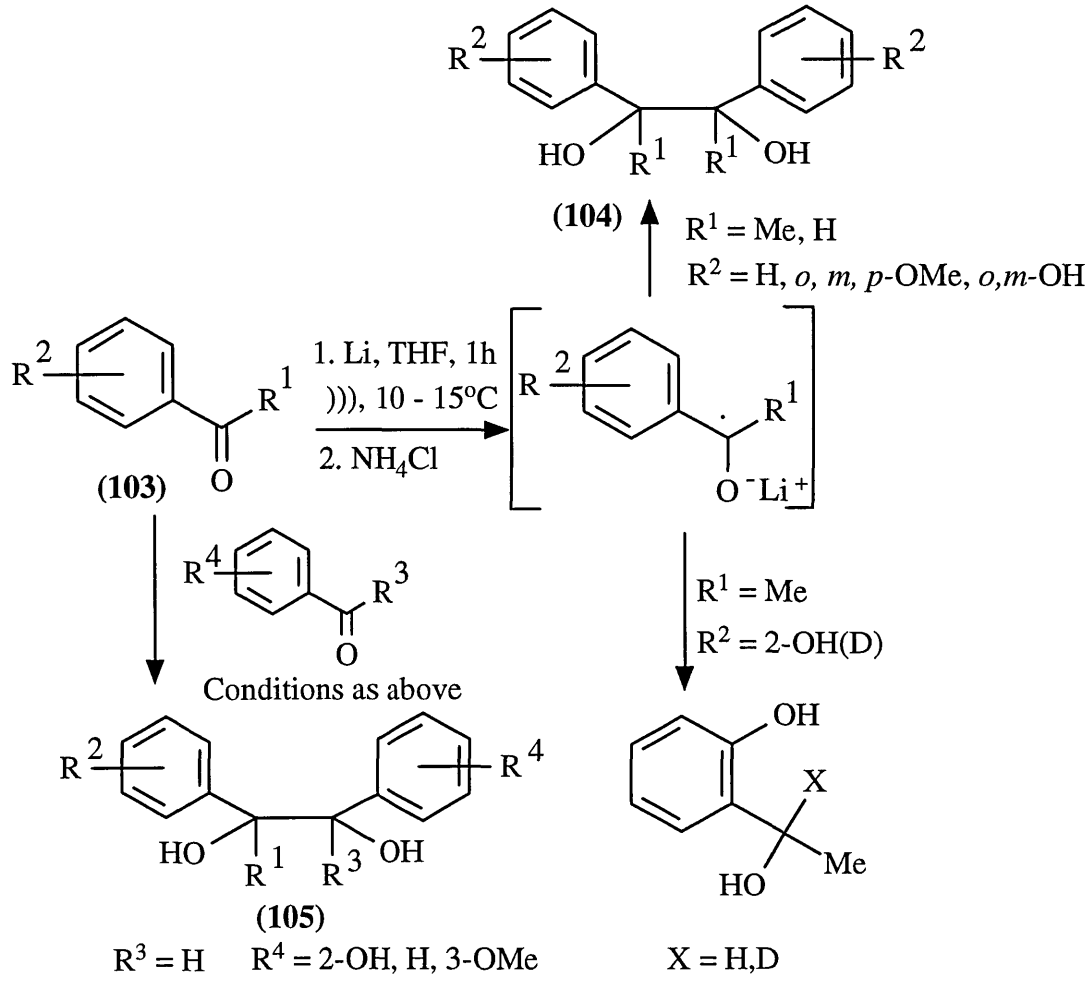
[Scheme 88]

Diphosphines can be prepared under similar conditions, and selectivity is improved by the capability of ultrasound to enable the reaction to be carried out at a lower temperature than standard [Scheme 89].



[Scheme 89]

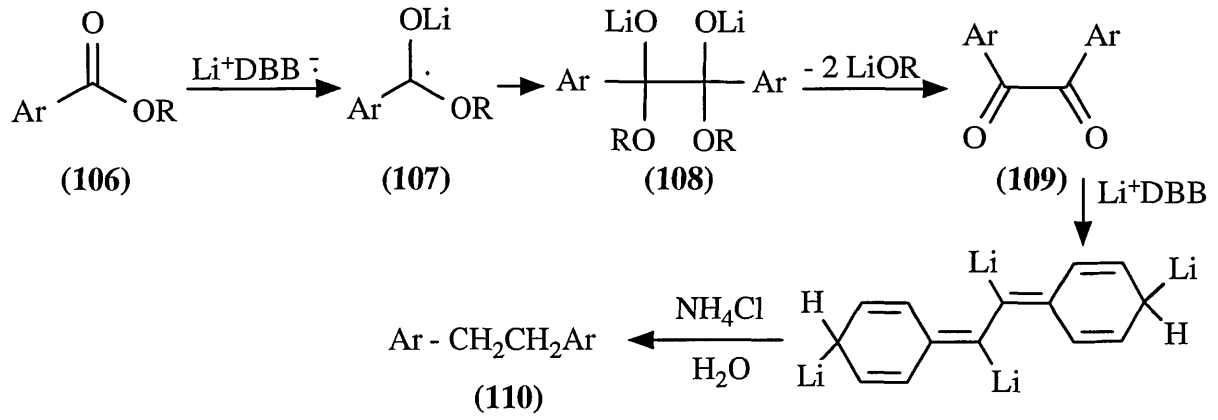
Sonochemical hydrodimerisation[261] of aromatic carbonyl compounds (**103**) to pinacols (**104**) has been achieved *via* ultrasonically generated ketyl radical anions, these are generated when aryl alkyl ketones are sonicated in the presence of ultrasound. This provides an alternative quicker and milder route to ketyl radical anions as opposed to photochemical or electrochemical methods. This method also allows the coupling of two different carbonyl compounds as seen by the synthesis of diol (**105**) [Scheme 90].



[Scheme 90]

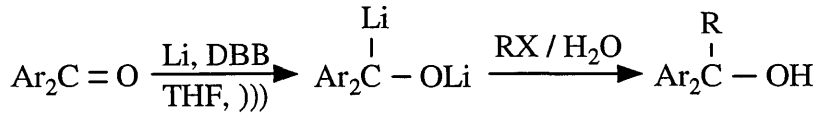
Electron Transfer Agent 4-4'-dibutylbiphenyl (DBB)

It has been reported that in the presence of ultrasound various substrates undergo reductive elimination with excess lithium in the presence of electron transfer agent 4,4'-dibutylbiphenyl (DBB) in tetrahydrofuran to produce bibenzyl in good yields[262-265]. Without DBB the reaction rate is slow which suggests it acts as an electron transfer agent from lithium to the carbonyl compounds. A mechanism for the reduction of the aromatic ester was proposed in which the ester **(106)** reacts with the radical anion $Li^+ DBB^{-\cdot}$ to form the resultant radical anion **(107)** which then dimerises to **(108)**. This intermediate then goes on to lose two equivalents of lithium alkoxide to form the diketone **(109)**. Further reaction through a series of intermediate steps gives the bibenzyl **(110)** [Scheme 91].



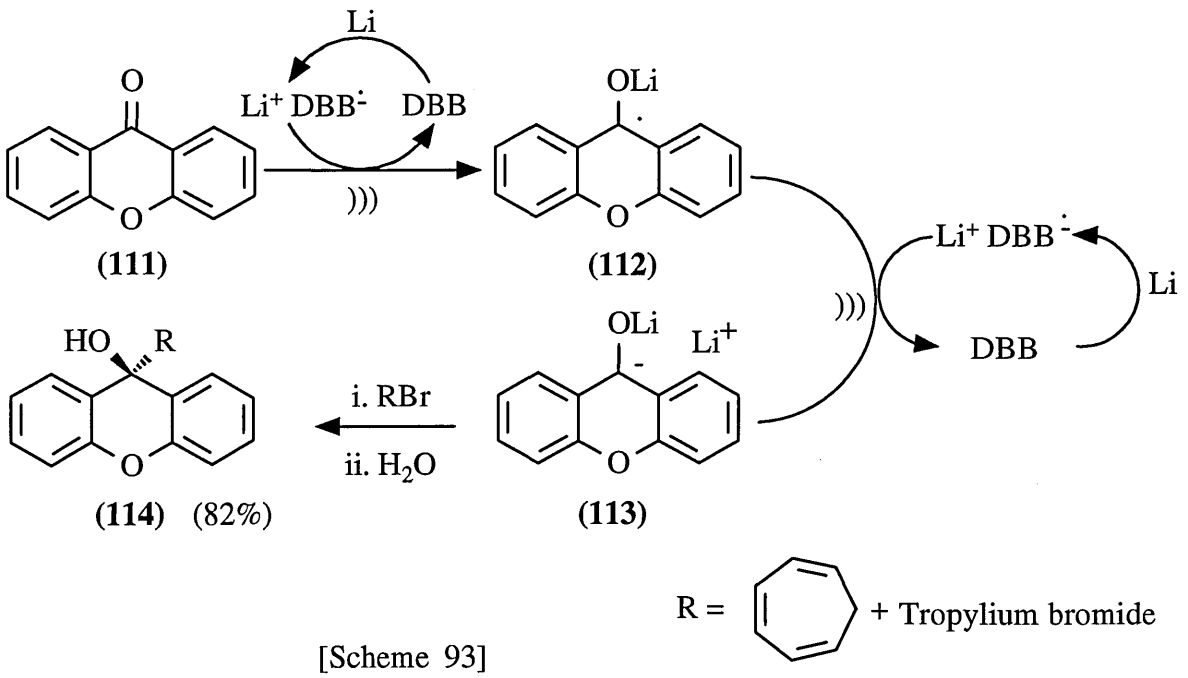
[Scheme 91]

When subjected to the same experimental conditions undergo aromatic ketones two successive single electron transfers to form a dilithium species that is reactive towards electrophiles[263,265] [Scheme 92].



[Scheme 92]

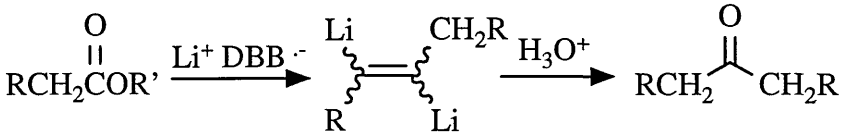
Compounds which are difficult to make by conventional methods, such as tricyclic **(114)** can be prepared from xanthen-9-one using this method [263,265]. This is due to the nucleophilic state of the carbonyl carbon. The xanthen-9-one **(111)** first of all accepts an electron from the lithium metal to become a ketyl anion **(112)** which then accepts a second electron to become a dianion **(113)** which then acts as a nucleophile[263] towards tropylium bromide to form the product in good yield [Scheme 93].



[Scheme 93]

If the reaction is continued over an extended time period the hydroxyl group can be reduced to the corresponding alkene[265].

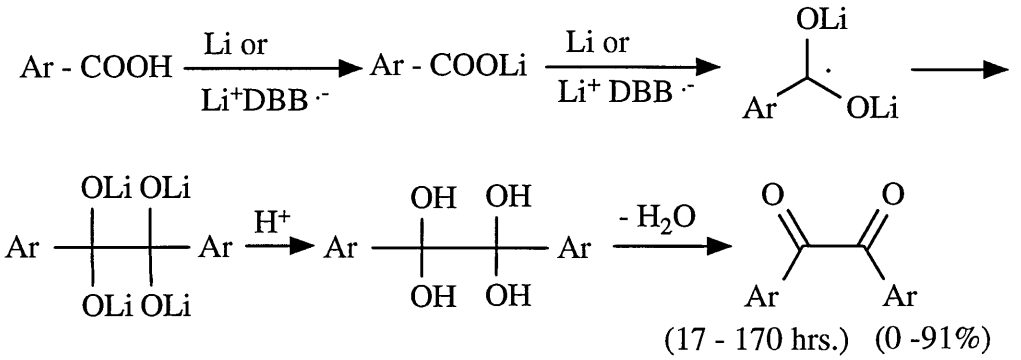
These experimental conditions can also be used to convert aliphatic esters with α hydrogens (RCH_2COOR') to the corresponding aliphatic ketones[264] (RCH_2COCH_2R) [Scheme 94].



[Scheme 94]

DBB transfers electrons from the lithium metal to the substrates in all the reactions in this section. When DBB is not added to the reaction the rate is slow, however the DBB anion radical forms very quickly with sonication when compared to about two hours for the stirred equivalent.

Aromatic α-diketones can be produced[266] from reaction of aromatic acids with either lithium 4,4'-di-t-butylbiphenyl radical anion or lithium metal [Scheme 95].



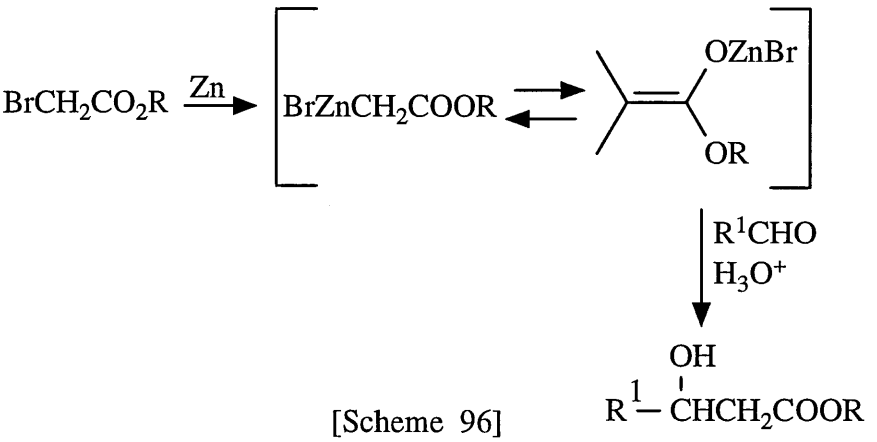
Ar = Benzoic acid, *m* & *p*-toluic acid, *p*-t-butyl benzoic acid, sodium benzoate, lithium benzoate

[Scheme 95]

With DBB the reaction rate was increased but overall yield decreased. Within the same time period it was found that there was little or no reaction with mechanical stirring.

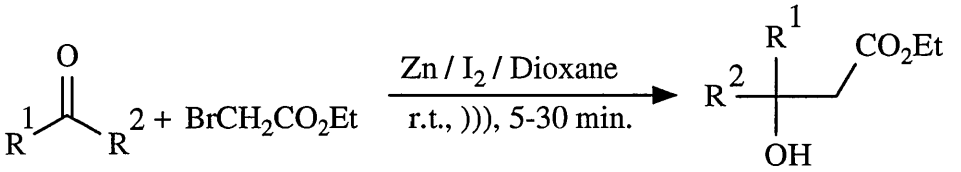
The Reformatsky Reaction

In the Reformatsky reaction a β-hydroxyester is prepared by treating an α-haloester with metallic zinc in the presence of a carbonyl compound. In the first step an organozinc derivative is formed from the α-haloester (which exists in equilibrium as an ester enolate) that then adds to the carbonyl compound to give the product [Scheme 96].



[Scheme 96]

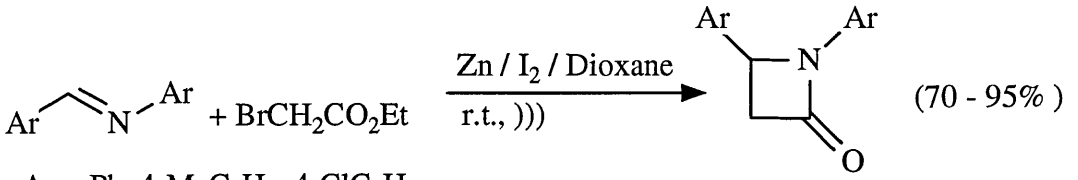
The application of ultrasound[267] to this reaction improves yields over conventional methods such as those using trimethylborate as cosolvent with activated zinc. Although dioxane has to be used instead of aromatic solvents and the zinc has to be activated with iodine, excellent yields of β-hydroxyesters can be produced within a short time [Scheme 97].



$R^1 = H$, $R^2 = (CH_2)_2CH_3$, R^1 & $R^2 = -(CH_2)_4-$ (97 - 98%)

[Scheme 97]

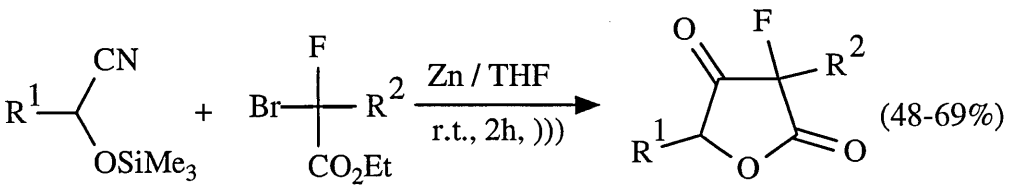
β-lactams can also be obtained in good yield when the Reformatsky reaction is applied to Schiff bases in dioxane at room temperature[268] under sonication [Scheme 98].



Ar = Ph, 4-MeC_6H_4, 4-ClC_6H_4

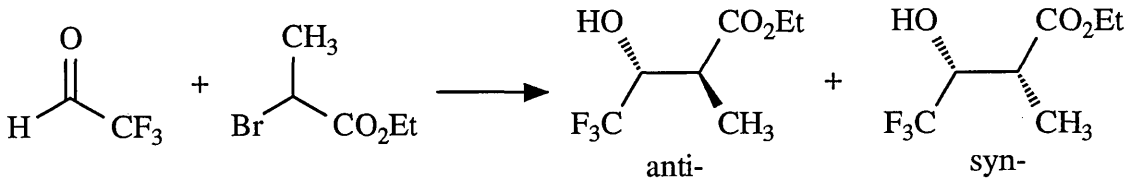
[Scheme 98]

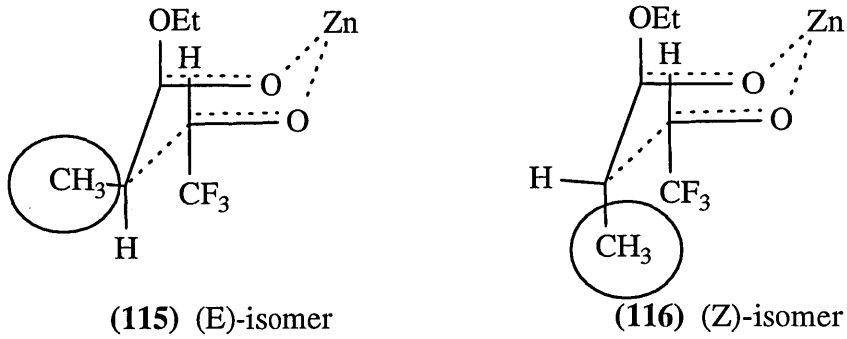
The Reformatsky reaction with nitriles produces imines which are readily hydrolysed to ketones . This reaction proceeds with ultrasound to give moderate yields[269] of keto-γ-butyrolactones.



$R^1 = CH_3$, Ph $R^2 = H$, CH_3

The Reformatsky reaction between trifluoroacetaldehyde and ethyl-2-bromopropionate has been studied, and in particular, the effect that ultrasound[196] has on the stereochemistry of the products. The geometry of the starting enolates geometry determined which stereoisomer is formed. The *anti* isomer is formed from the (E)-enolate and the *syn* isomer from the (Z)-enolate *via* a pericyclic transition state. The transition state that is formed from the (E) isomer **(115)** is considered to be of lower energy than the (Z)-isomer **(116)** [Scheme 99]. This is mainly due to the position of the methyl group which is in an equatorial position in the (E)-transition state whereas it is in a more crowded and less stable axial position in the (Z)-configuration. Thermodynamically the *anti* isomer is less stable than the *syn* isomer that is produced in this reaction. Therefore thermodynamically the *syn* isomer is favoured whereas the *anti* is favoured kinetically. This reaction can therefore serve as an indicator of increased kinetic or thermodynamic control of the system.





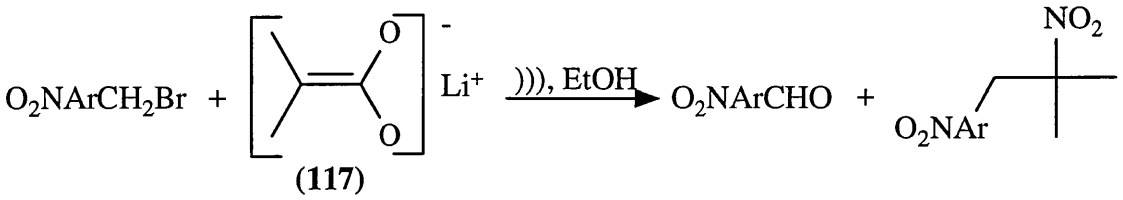
(115) (E)-isomer **(116)** (Z)-isomer

[Scheme 99]

For the silent reaction it was found that the products were racemic suggesting both kinetic and thermodynamic control. However, the stereochemistry is altered when ultrasound is emitted into the reaction. The β-hydroxyesters produced have moderate *anti*-selectivity (73% *anti* versus 27% *syn*) and the authors state that this indicates the increased kinetic control when ultrasound is used, which favours production of the (E)-enolate.

The Kornblum-Russell Reaction

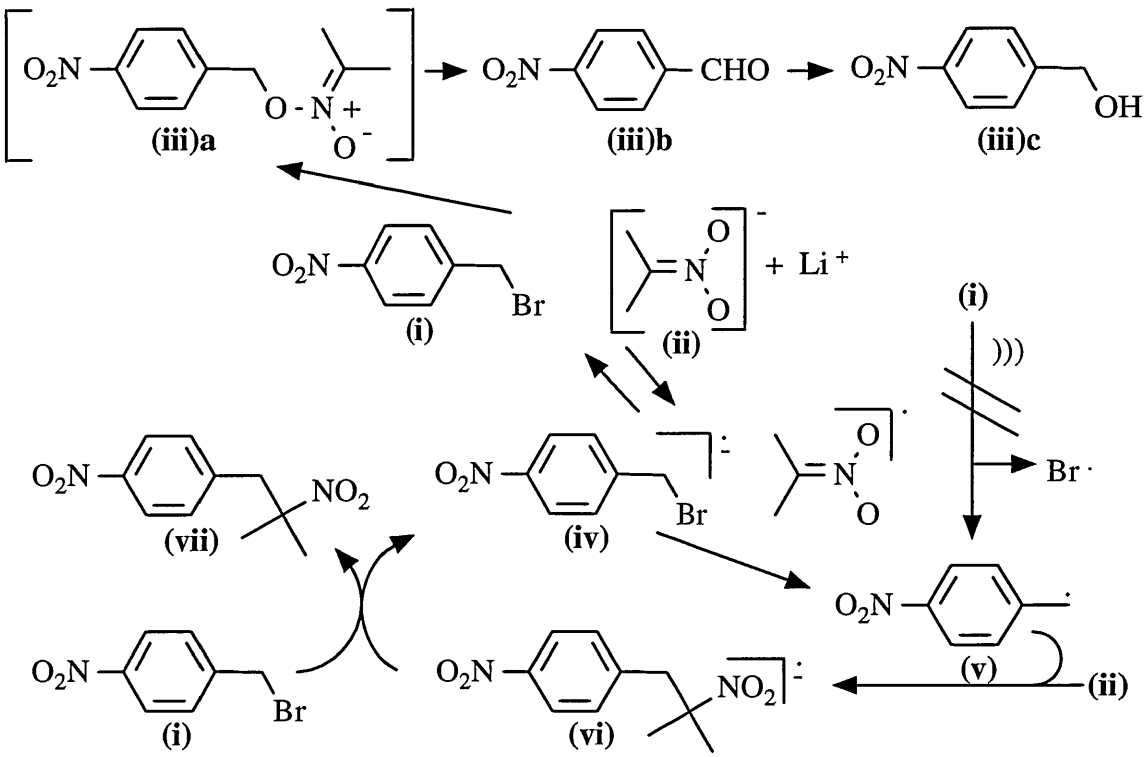
Ultrasound also directly influences[270] the Kornblum-Russell reaction. The study of this reaction has provided further proof of the electron transfer enhancing effect that ultrasound has on reactions. Sequential electron transfer processes are favoured by ultrasound[173,178] to the detriment of polar (simultaneous bielectronic) reactions. The reaction studied is the Kornblum-Russell alkylation of nitronate anions[271,272] **(117)**. Specifically the reaction with the lithium salt of 2-nitropropane and p-nitrobenzyl bromide [Scheme 100].



(117)

[Scheme 100]

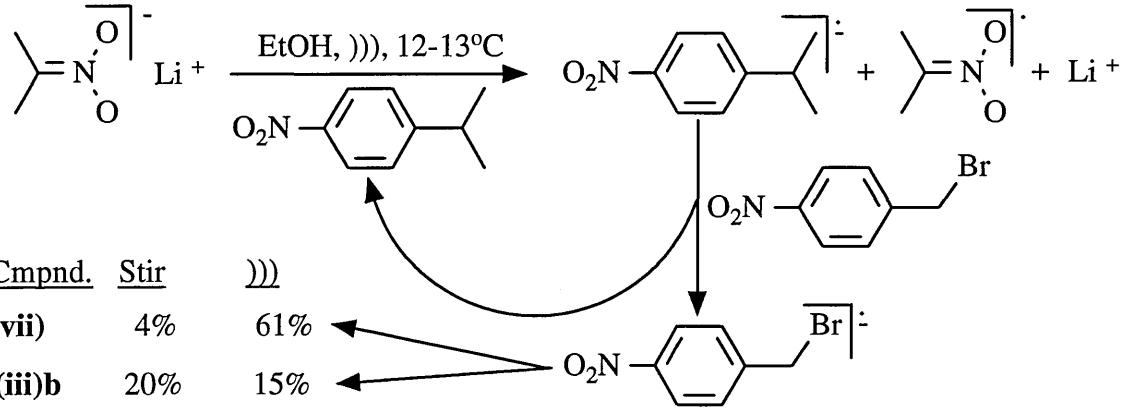
The mechanism for this reaction is detailed below [Scheme 101].



[Scheme 101]

Adapted from M.J.Dickens, J.L.Luche, *Tetrahedron Lett.*, **32**, 4709, 1991.

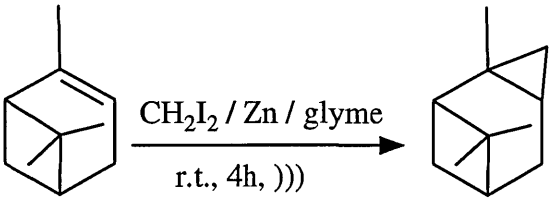
This scheme illustrates how **(iii)b** is obtained from an ionic mechanism whereas **(vii)** arises from an electron transfer mechanism. In the absence of sonic waves it was found that the O-alkylation product predominates with a ratio of **(vii)**:**(ii)b** = 0.1 to 0.2, which agrees with the authors' prediction that the polar mechanism is not accelerated by sonication. When the reaction mixture is irradiated with ultrasound (30kHz) the ratio of **(vii)** in the product mixture increases indicating that ultrasound strongly influences the pathway proceeding *via* a sequential electron transfer. In the same experiment it was found that when conditions were altered to produce standing waves the yield of **(vii)** was increased further which is in agreement with other previous work[273,274]. It was also found that sonolysis of **(i)** will not produce **(v)**, discounting any theory of direct initiation of the starting material to the radical species **(v)**. This demonstrates that **(v)** must be produced *via* the reaction between **(i)** & **(ii)**. However this reaction (electron transfer) between **(i)** & **(ii)** is too endergonic to occur spontaneously when they are in their ground state[275], therefore one of these species has to be excited by ultrasound to promote the formation of **(v)**, the mechanism of which is unknown. Alternatively the reaction can be made easier with the addition[276] of a mediator. This was found to have an effect on the previous reaction when 4-nitrocumene was added[270] [Scheme 102].



[Scheme 102]

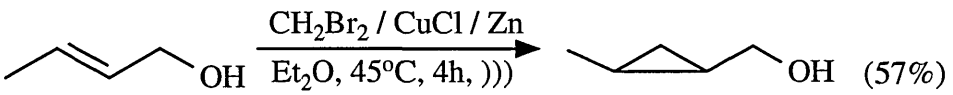
Simmons-Smith Cyclopropanation

In the sonochemical[277] alternative of the Simmons-Smith cyclopropanation to compound **(118)** it was found that the induction period was reduced, increased control of the process, reproducibility, high yields and the use of low grade mossy zinc was possible with the application of ultrasound.

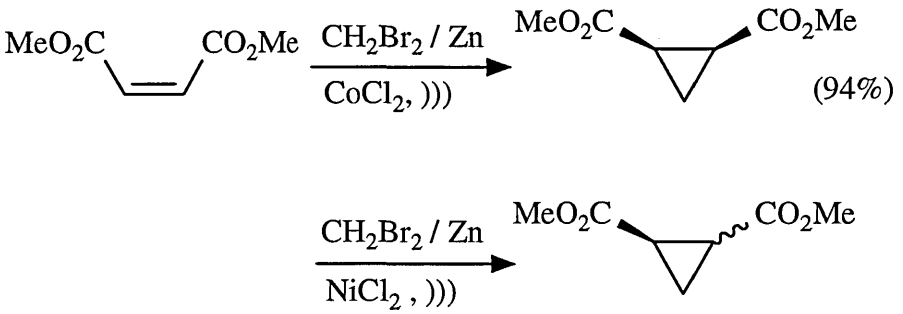


(118)

The reaction can also be modified[278] to run with the cheaper reagent dibromomethane rather than di-iodomethane.



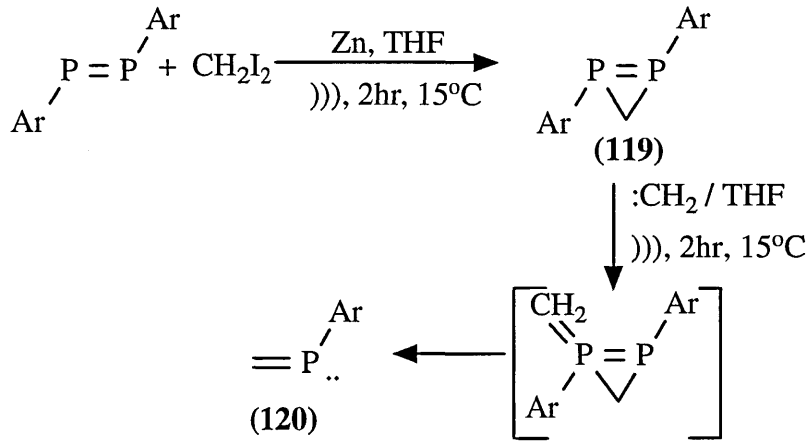
The catalyst used can affect[279] the stereoselectivity of this type of reaction. When cyclopropanation of dimethyl maleate with zinc and dibromomethane is catalysed with cobalt chloride the reaction is stereoselective, whereas when nickel chloride is used no stereoselectivity occurs [Scheme 103].



[Scheme 103]

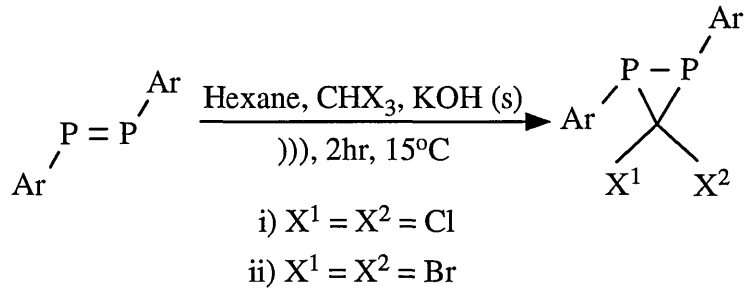
Diphosphines can also undergo Simmons-Smith cyclopropanation[219] using regular zinc powder in THF in the presence of di-iodomethane to produce diphosphirane **(119)**. Under ultrasound **(119)** reacts with excess methylene diradical to generate the phosphalkene **(120)**, [Scheme 104].

It is believed the reaction proceeds as a result of the zinc being activated by the ultrasound. The silent equivalent requires the zinc to be pre-activated.



[Scheme 104]

Cyclopropanation of diphosphines with halogenocarbenes was also described[219] as a route to diphosphiranes. The diphosphine was sonicated with KOH and a haloform in hexane to give the desired product in quantitative yields, whereas the silent reaction required n-butyllithium or freshly sublimed potassium t-butoxide [Scheme 105].

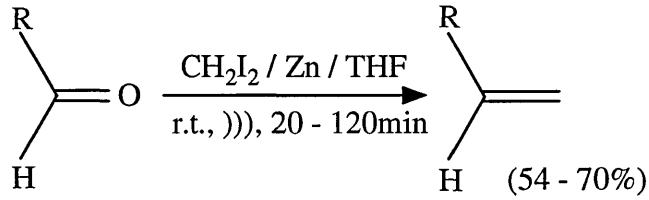


[Scheme 105]

As a supplement to the phosphine chemistry the preparation of phosphine, PH_3, from red phosphorus and its subsequent alkylation by terminal alkenes and alkynes in basic media leading to the corresponding aliphatic and vinylic derivatives in two steps or one-pot reaction[280] was found to be improved by the application of ultrasound.

Methylenation of Carbonyls

The Simmons-Smith reagent of zinc and di-iodomethane can be used to methylenate carbonyl groups[281] with sonication. The reaction proceeds with good yield in most cases except with ketones which do not yield the expected products satisfactorily [Scheme 106].

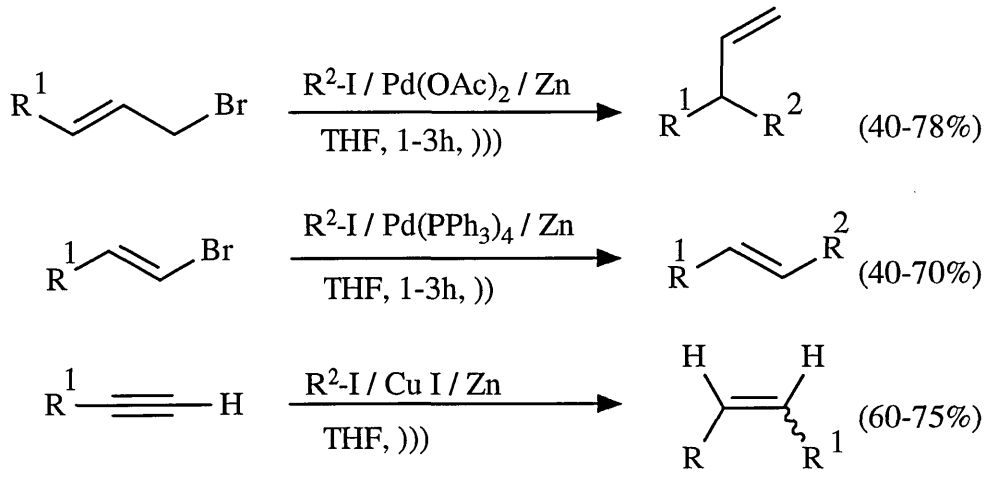


R = 1-naphthyl, Ph, $(CH_2)_5CH_3$

[Scheme 106]

Perfluoroalkyl Derivatives of Unsaturated Compounds

The preparation of perfluoroalkyl zinc derivatives and their *in situ* reaction[282] with allyl and vinyl halides, alkynes and dienes has been reported. However sonication does not solely produce a significant effect on the reaction and it has to be used in conjunction with a catalyst [Scheme 107].



R^1 = CH_3, Ph R^2 = perfluoroalkyl

[Scheme 107]

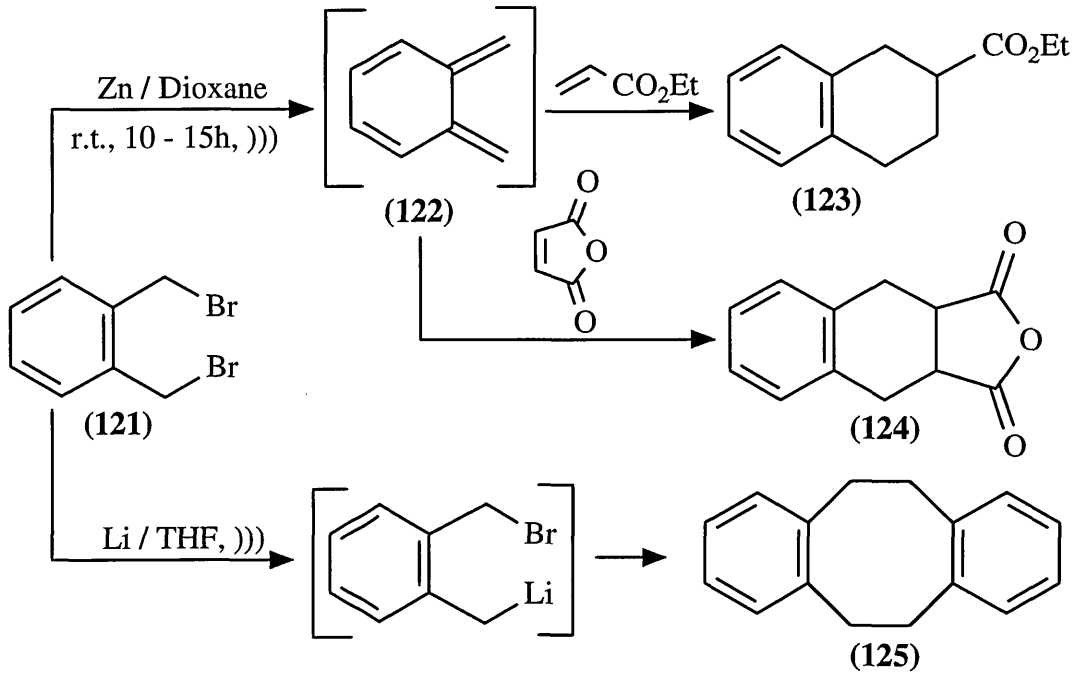
Perfluoroalkyl carboxylic acids can also be prepared[283] in moderate yields from the same reagents by trapping them with carbon dioxide using dimethylformamide as a solvent.

$$RI \xrightarrow[)))]{CO_2 / Zn / DMF} RCO_2H$$

R = perfluoroalkyl, perfluoroalkenyl

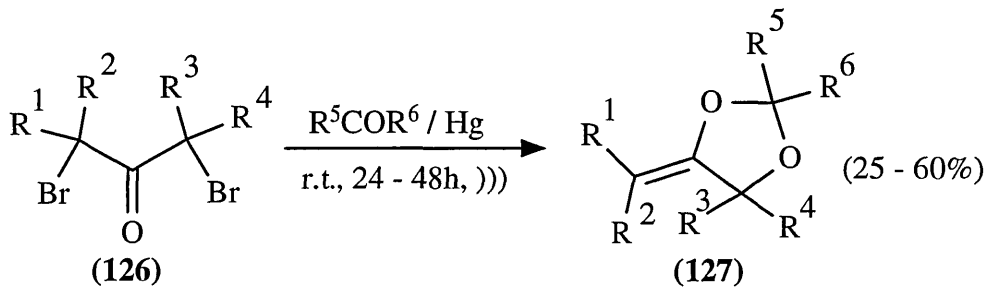
Cycloadditions

Ultrasonic irradiation[284] of α-α'-dibromo-o-xylene **(121)** with zinc in dioxane yields a xylylene intermediate **(122)** which will add *in situ* to dienophiles present in the reaction mixture to afford the polycyclic compounds **(123 & 124)** in good yield. This reaction does not proceed without ultrasonic irradiation. Polymer and a small amount of the dimer are formed in the absence of any dienophile. A good yield of the dimer **(125)** is obtained if the zinc is substituted with lithium [Scheme 108].



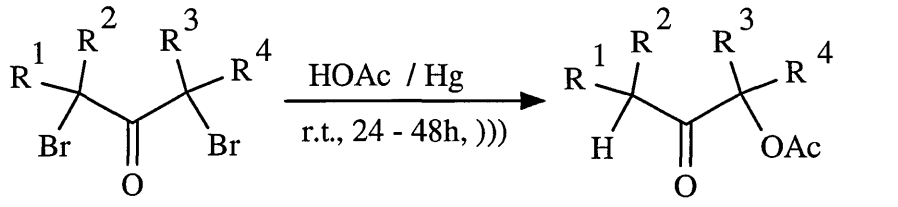
[Scheme 108]

Other dibromo compounds have been used successfully in cycloadditions. α,α'-Dibromoketones (**126**) were used[285] to prepare dioxolanes (**127**) in moderate yields. The chief advantage of ultrasound was in efficiently preparing emulsions of the mercury used as catalyst.



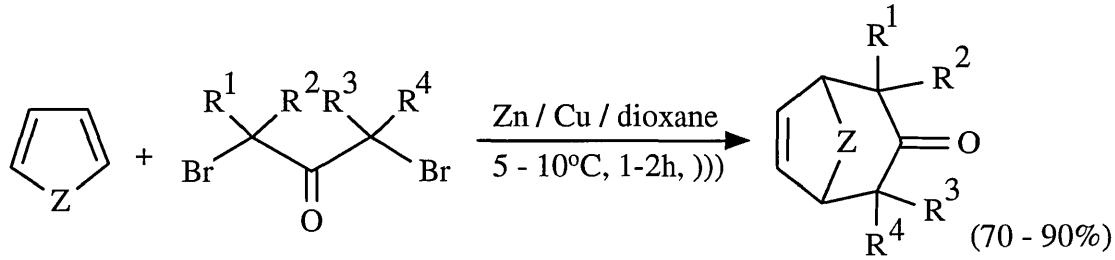
(**126**) (**127**)

This method was also used to prepare α-acetoxy ketones[286] (**128**) in moderate to good yields.



(**126**) (**128**) (40 - 92%)

In a similar reaction α,α'-dibromoketones (**126**) were used to prepare organozinc reagents[287] that were used to add to various dienes to form the cyclic compound (**129**). Compared to conventional methods the conditions were milder and activation with chlorotrimethylsilane was not required [Scheme 109].

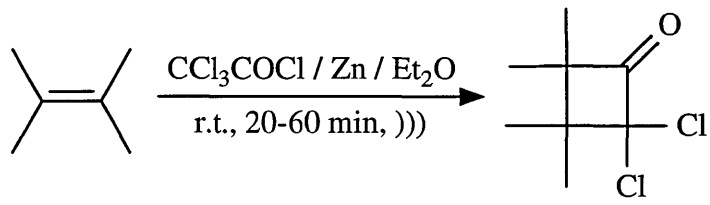


(**126**) (**129**)

$R^1, R^2, R^3, R^4 = CH_3, -(CH_2)_n-, H$ $Z = CH_2, O$

[Scheme 109]

Cyclobutanones (**130**) can be prepared[288] both by *in situ* generation of dichloroketenes and cycloaddition to alkenes under sonication and by conventional methods. However sonication increases yields and/or reaction rate [Scheme 110].



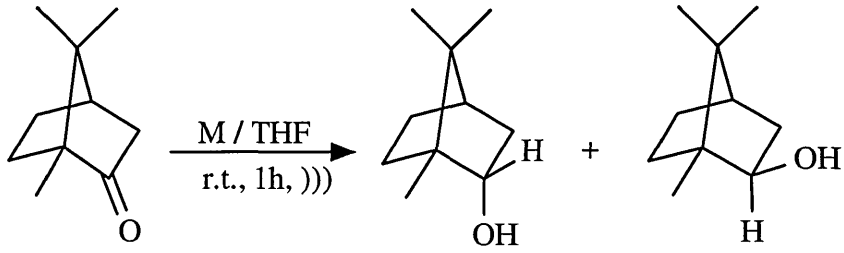
(130)

Substrate	Stir (time/h)	Yield)))
Indene	80 (2)	80
Cyclopentene	22 (7)	70
Norbornene	70 (12)	75

[Scheme 110]

Single Electron Transfer (SET) Reactions Using Metals Carbonyls

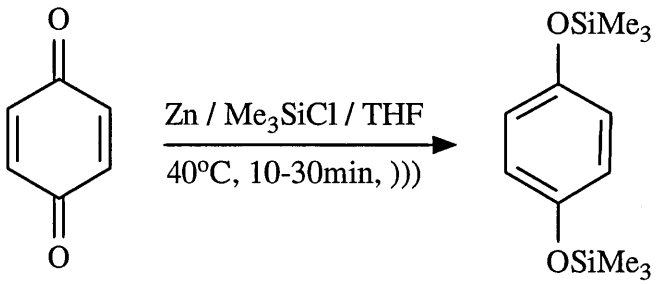
Camphor can be reduced to endo and exoborneol[289] using alkali metal in THF suspension with ultrasound. The excess of the endo product depends on the alkali metal. The reaction is believed to proceed *via* a single electron transfer mechanism [Scheme 111]. No comparison to the quiet reaction was discussed in the paper.



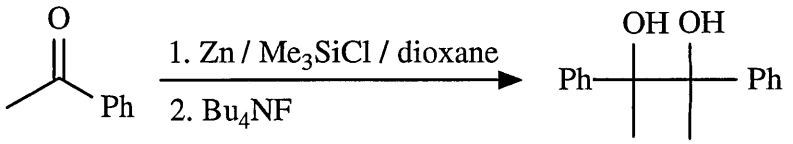
Metal	% Endo
Li	73
Na	68
K	42

[Scheme 111]

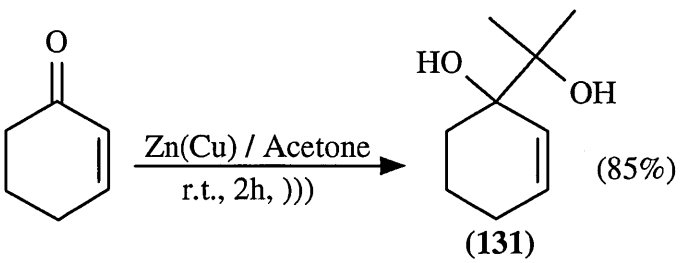
Other carbonyl compounds such as quinones can be reduced with trimethylchlorosilane and zinc under sonication[290] with good yield.



High yields of pinacols are obtained when α-unsaturated carbonyl compounds are sonicated with zinc and trimethylchlorosilane in dioxane[291] followed by hydrolysis with tetrabutylammonium fluoride. This compares well with conventional methods which tend to yield complex mixtures. The exception to the advantage gained using ultrasound is when β-aryl-substituted substrates are used. Aryl ketones can be reductively coupled using zinc and trimethylchlorosilane in THF.

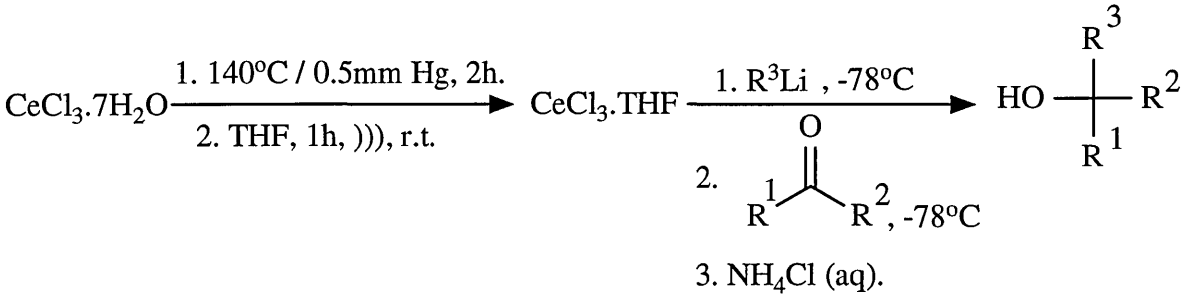


In an unusual reaction[292] two carbonyl compounds are coupled when cyclohexene-2-one is reduced and the solvent acetone adds to the compound to yield the pinacol **(131)**.



(131)

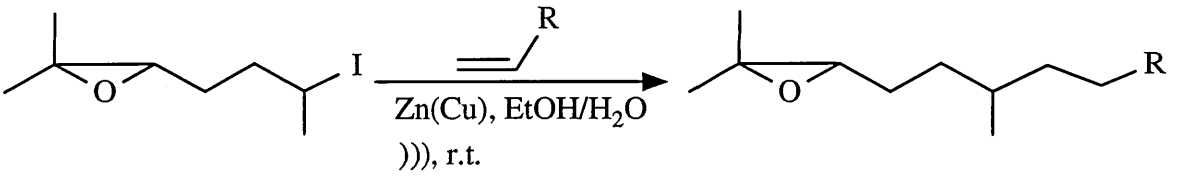
Ultrasound is used to obtain a more homogeneous suspension in the preparation of organocerium reagents from anhydrous cerium chloride and organolithium. These can be used to add to a wide range of carbonyl compounds[293] in high yields [Scheme 112]. This preparation compares favourably to the stirred reaction which has to be run overnight.



[Scheme 112]

Epoxy Compounds

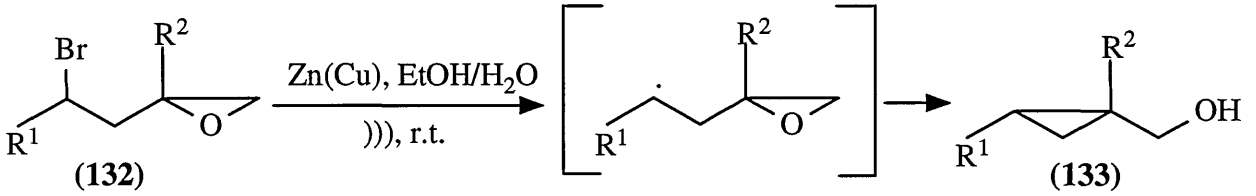
Zinc-copper couple in aqueous ethanol under sonication[294] induces the conjugate addition of epoxyalkyl halides to α-β-unsaturated carbonyl compounds [Scheme 113].



R = COMe (80%) R = CO_2Me (74%) R = CN (81%)

[Scheme 113]

However, when the reducible groups are less than two carbons apart, as in compound **(132)**, cyclopropyl alcohols **(133)** are formed instead of the conjugate addition product. The mechanism below is suggested [Scheme 114].

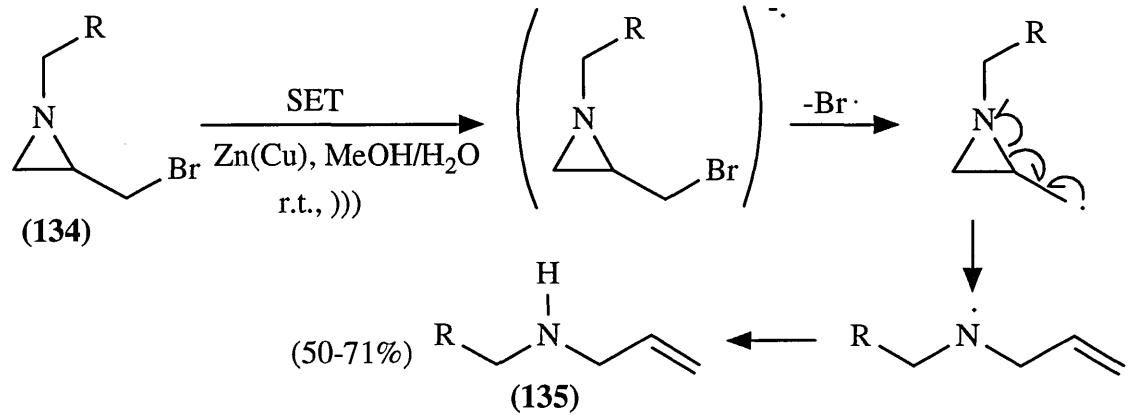


[Scheme 114]

Ultrasound[173] is believed to promote such electron transfers at the surface of reducing metals.

Aziridines

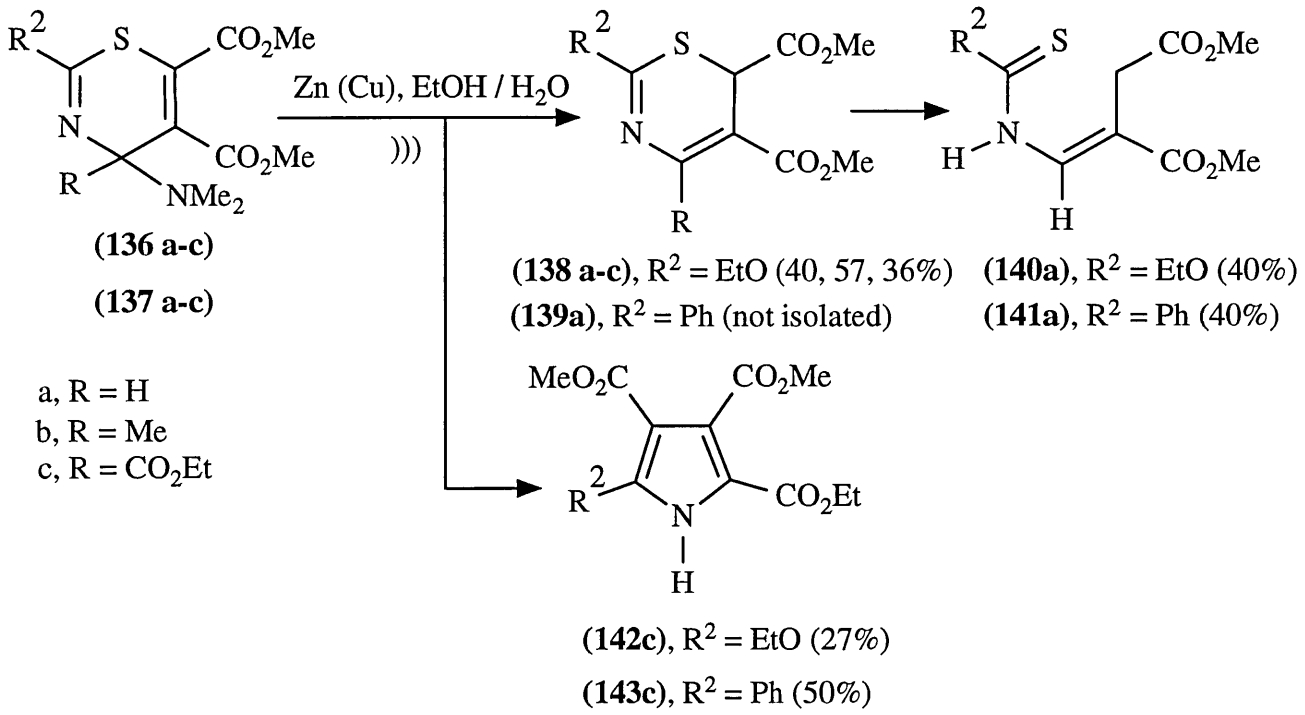
The sonochemical cleavage[295] of 2-(bromomethyl)aziridines **(134)** by a zinc-copper couple into allylamines **(135)** results in a clean reaction with no side reactions. The mechanism occurs *via* a SET from the metal to the substrate [Scheme 115].



R = Ph, 4-MeC_6H_4, 4-ClC_6H_4, $CHEt_2$, $CHMe_2$

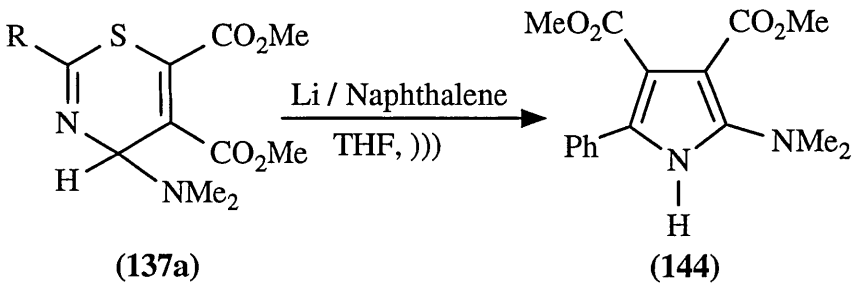
[Scheme 115]

Although no silent reactions are discussed several reductions (using Zn-Cu or lithium-naphthalene) of substituted 4H-1,3-thiazines **(136 & 137)** have been reported[296]. Selectivity leading to substituted 6H-1,3-thiazines **(138 & 139)** and its derivatives **(140 & 141)** or pyrroles **(142 & 143)** by sulphur extrusion is dependent on the substitution of the 4H-1,3-thiazine derivatives. Treatment of the substituted 4H-1,3-diazines with an aqueous ethanolic Zn-Cu couple under ultrasound leads to the corresponding 6H-1,3-thiazines **(138 a-c)** and **(139a)**. Formation of the substituted carbamates **(141a)** or thiobenzamide can result from reductive ring cleavage. Formation of 5-(ethoxycarbonyl)pyrroles **(142c)** & **(143c)** has also been observed under these conditions [Scheme 116].



[Scheme 116]

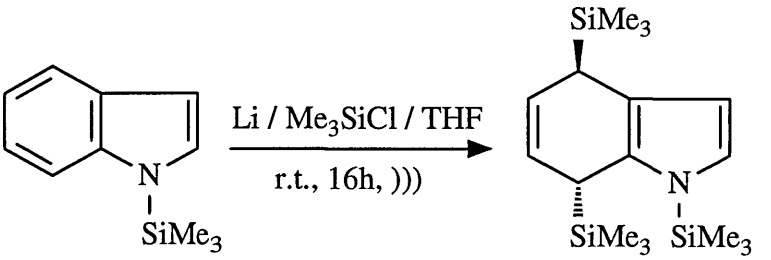
If the conditions are changed and 2-phenyl-4H-1,3-thiazine **(137a)** is sonicated with lithium (2 equivalents) and an electron transfer agent (naphthalene) in THF the substituted 5-(N,N-dimethylamino)-2-phenylpyrrole **(144)** is produced. Non-selective reactions occur with compounds **(136a-c)**.



The authors postulate the formation of **(144)** *via* a carbanionic intermediate. These reactions are compared with reduction in zinc/acetic acid by conventional methods which results in the reduction of the thiazine to **(138a-c)** as before when R^2 = EtO and production of pyrroles when R^2 = Ph. The authors state the electron transfer process leading to an anion radical is favoured by the ultrasonic methods but have not shown direct comparisons to the silent reactions under identical conditions.

Unsaturated Bonds

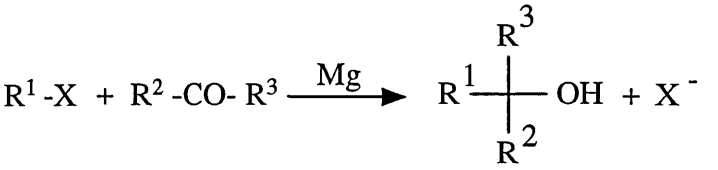
Reduction of double bonds[297], alkynes[298], and aromatics[299] using metals with ultrasound have been reported. For example, the N-protected indole **(145)** undergoes reduction to the dihydro compound **(146)** when it is sonicated with lithium and trimethylchlorosilane. Without sonication the rate and yield are significantly decreased .



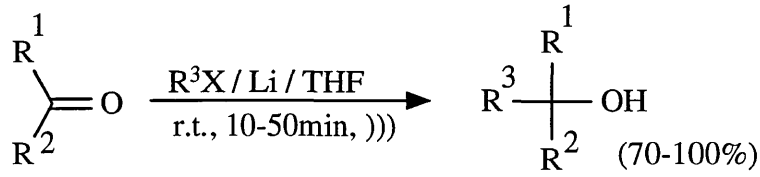
(145) **(146)**

1.3.8 THE BARBIER REACTION - One Step Generation & Reaction of Organometallics

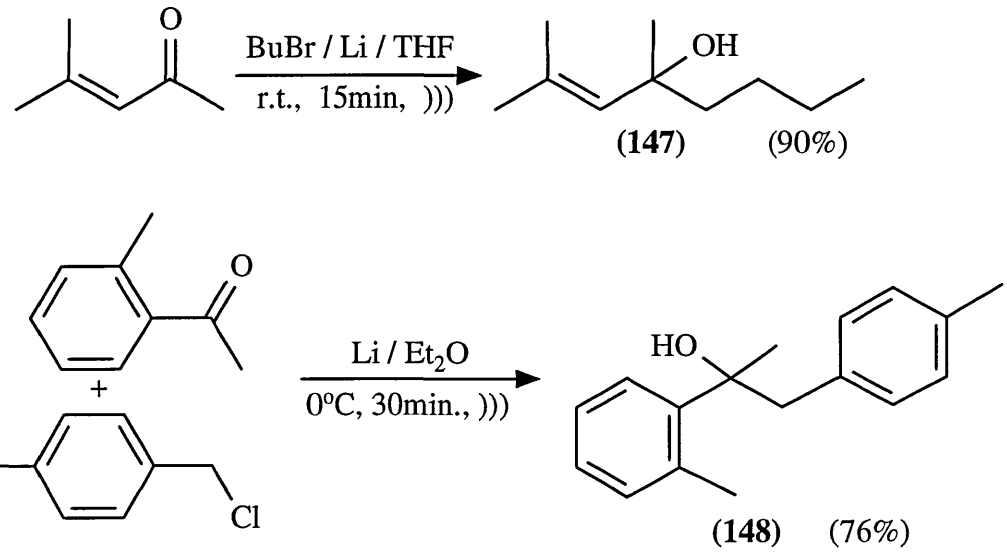
Barbier[300] made an important contribution to organometallic chemistry by discovering the one step process where alkyl halides, carbonyl compounds and magnesium react to produce an alcohol.



The Barbier reaction has the advantage of preparing the organometallic reagent in the presence of the substrate, which affords the possibility of utilising unstable organometallics and considerable time saving. The disadvantage of the Barbier reaction is that it proceeds only with more reactive alkyl halides that possess good leaving groups. This can be improved by substituting the magnesium with lithium[301], but the reaction is improved immensely[234] when it is subjected to ultrasonic irradiation. Even using damp THF, alcohols can be obtained in good yields from reaction with various aldehydes and ketones.

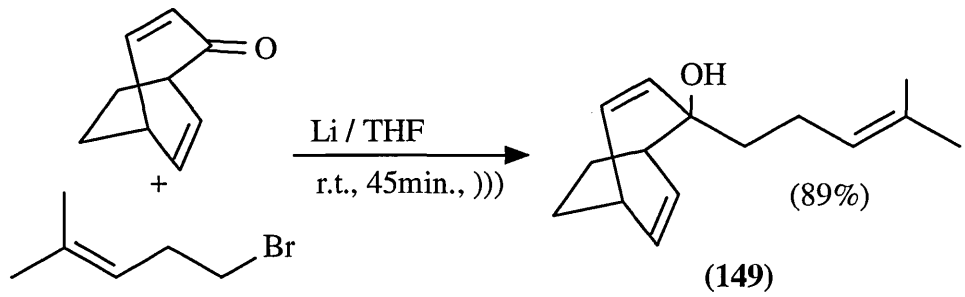


Benzyl and allyl halides when used as a substrate lead to good yields[302,303] of the alcohols **(147)** and **(148)** and the unwanted Wurtz-coupling side reaction is suppressed [Scheme 117].

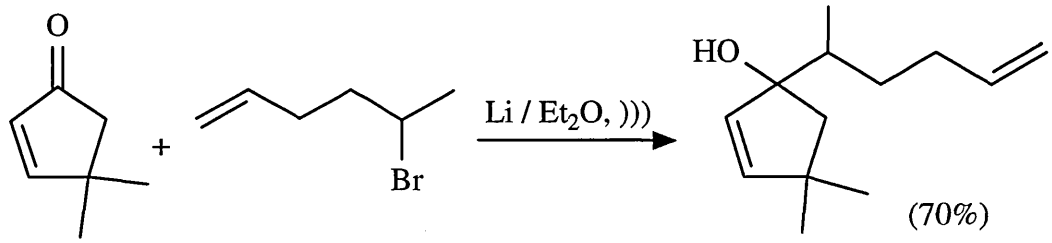


[Scheme 117]

More complicated intermediates such as **(149)** can be prepared using a sonochemical[304] Barbier method.

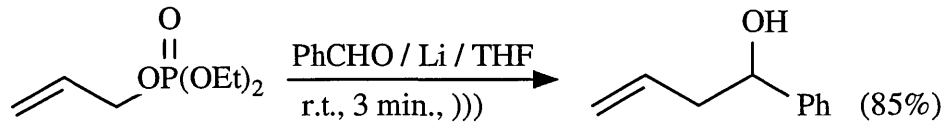


Also the synthesis of pentalenic acid can start with the sonication of dimethylcyclopentenone, 5-bromo-1-hexene, and lithium[305] to produce the intermediate **(150)**.

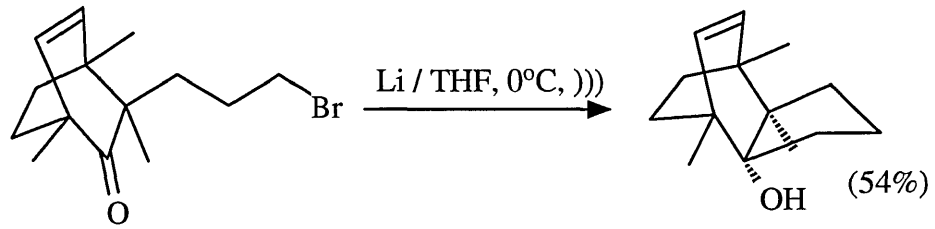


(150)

Allylic phosphates can be used instead of halides. These are reacted it with benzaldehyde and lithium under sonication in THF to produce the corresponding alcohol[306] in good yield.

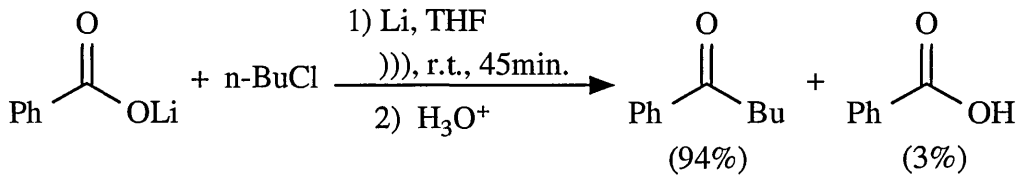


Intramolecular reactions have also been reported[307] where the molecule contains a carbonyl group and a halogen as in compound **(151)** which cyclises to form compound **(152)**.



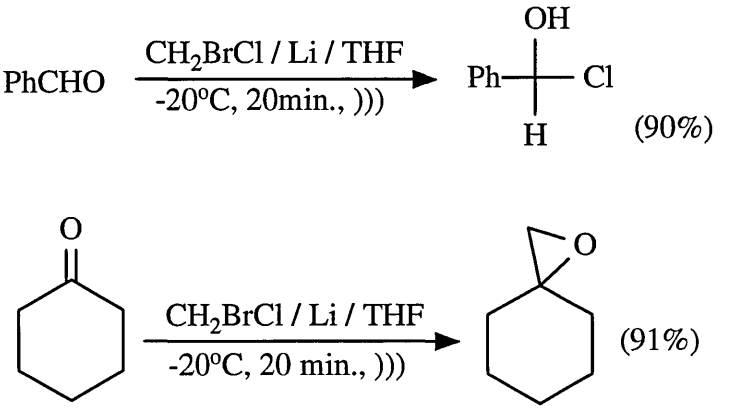
(151) **(152)**

The Barbier reaction has been used successfully under sonochemical conditions[308] to afford ketones from carboxylate salts. Sonication of n-butyl chloride, lithium benzoate and lithium metal in THF at room temperature affords the ketone in good yield [Scheme 118]. The authors carried out the experiment using other butyl halides which afforded reduced yields and other by-products (t-alcohols, diketones, and acids).



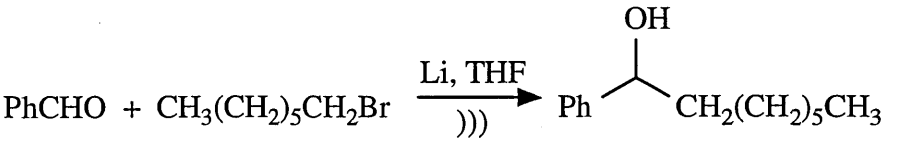
[Scheme 118]

The advantages of the one step Barbier process have been applied to the generation of the unstable organometallic reagent chloromethyllithium ($ClCH_2Li$). This reagent is usually prepared from chloroiodomethane and butyllithium but sonication allows the cheaper substitution of bromochloromethane and lithium for an *in situ* reaction. Epoxides are obtained in high yields from ketones[309] whereas depending on their structure aldehydes produce epoxides or chlorohydrins [Scheme 119].



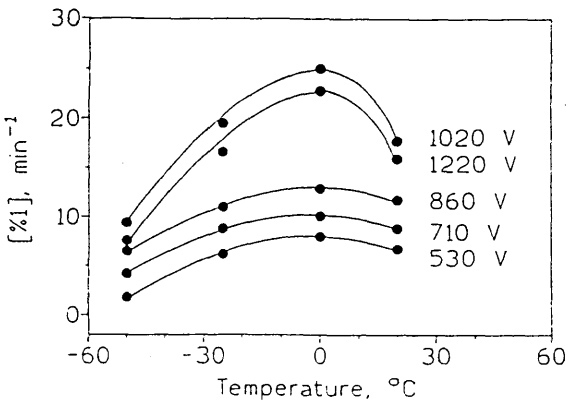
[Scheme 119]

Luche *et al*[310] have studied the mechanism by which ultrasound is effective on the modified Barbier reaction with lithium. The reaction of benzaldehyde and n-bromoheptane with lithium in THF under ultrasound at various acoustic energies and various temperatures was investigated.



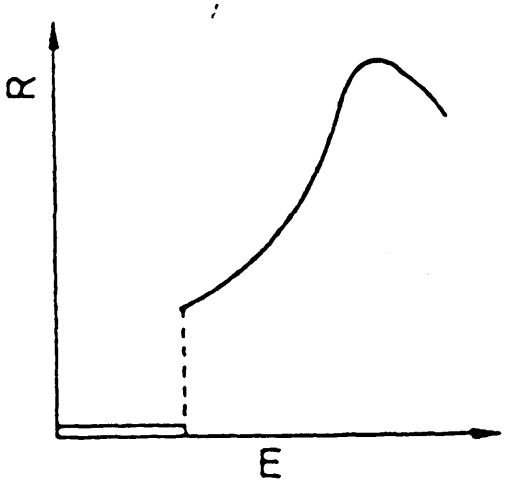
It was found that as temperature was decreased from 20 to 0 °C the reaction rate increased (which is a further illustration of what Luche describes[310] as the "paradoxal effect") where a lowering of the solvent vapour pressure produces a more energetic cavitational collapse [Figure 1.16]. A further decrease in temperature leads to a decrease in reaction rate which is attributed to an increase in viscosity which reduces bubble formation efficiency and hence leads to a decrease in intensity of bubble collapse.

Figure 1.16 Temperature vs. Reaction Rate[310]



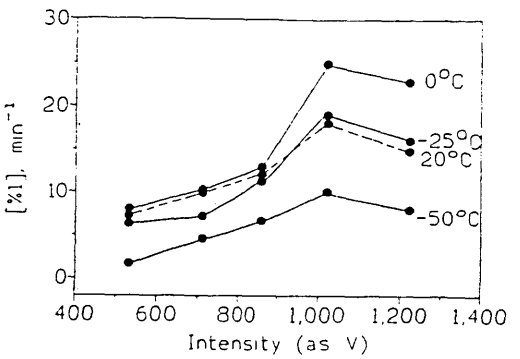
It was found in the same study that intensity of ultrasonic irradiation had a significant effect on the reaction rate [Figure 1.17]. As expected a minimum intensity was required before any reaction occurred, since a minimum intensity is required to produce cavitation. This shows a direct link between cavitation and reaction rate i.e. no cavitation - no reaction. When the intensity was increased the reaction rate also increased as the cavitation collapse becomes more violent. However a maximum rate versus intensity was reached after which the rate decreased with increase in intensity, due to over-production of bubbles which disperse the acoustic energy and mask the propagation of ultrasound waves throughout the medium.

Figure 1.17 Intensity vs. Reaction Rate[310]



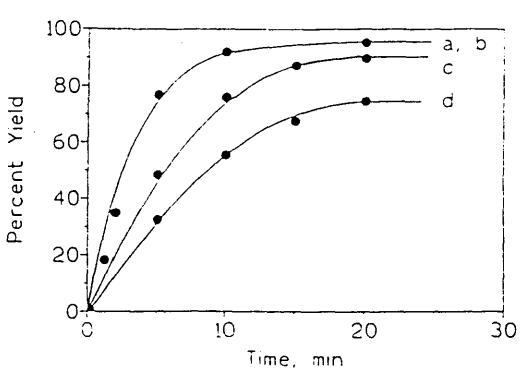
These two effects of temperature and intensity can be illustrated in a combined plot of both [Figure 1.18].

Figure 1.18 Temperature/Intensity/Reaction Rate[310]



The Barbier reaction only proceeds if the metal surface has exposed atoms at defects such as microcracks and dislocations, which allow single electron transfers[311,312] to individual carbon - halogen bonds in the organic halides. Ultrasonic irradiation results in activation of the metal surface, but this effect is not solely the cause for the rate enhancement. It was shown that ultrasound enhances the SET between the metal and carbon - halogen bond. Although the exact nature of this is still to be determined, the role of ultrasound is shown not to be of a simple "super agitation" but exerts a direct chemical effect. To illustrate this the percentage yield of alcohol versus time is compared at high and low intensities in the presence of ordinary or pre-activated (pre-sonicated) lithium [Figure 1.19].

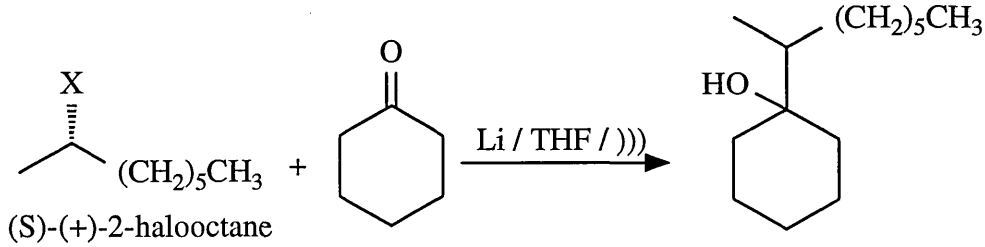
Figure 1.19 Percentage Yield vs. Activated Lithium[311]



a = Li not preactivated, 1020 V intensity; b = Li preactivated, 1020 V intensity; c = Li preactivated, 530 V intensity; d = Li not preactivated, 530 V intensity.

Pre-activating the lithium has no difference on the reaction when high intensity ultrasound is used,indicating that active sites are produced very rapidly. However, when low intensity ultrasound with the pre-activated lithium is used the rate is reduced, which suggests the rate is proportional to the intensity of ultrasound. These results illustrate a direct chemical effect on SET from the sonication of the reaction. The slowest rate is from the low intensity ultrasound with non-preactivated lithium which shows that the formation of active sites and SET are both reduced at low intensity.

Another Barbier reaction involves optically active octyl halides and cyclohexanone[313] which react with lithium in THF to yield optically active products. Sonication of this Barbier reaction affects both the stereochemistry and the enantiomeric excess of the products. This relationship between acoustic energy and enantiomeric excess has led the authors to believe that the reaction does not proceed *via* an organometallic reagent, but directly to the formation of radical species which can then react with the carbonyl group in several ways. Using bromo-, chloro- and iodo- (+)-(S)-2-octyl halides under various conditions it has been shown[311] that chloro and bromo alkyl halides lead to optically active products **(153)** and the iodo alkyl halide produces a racemic mixture.

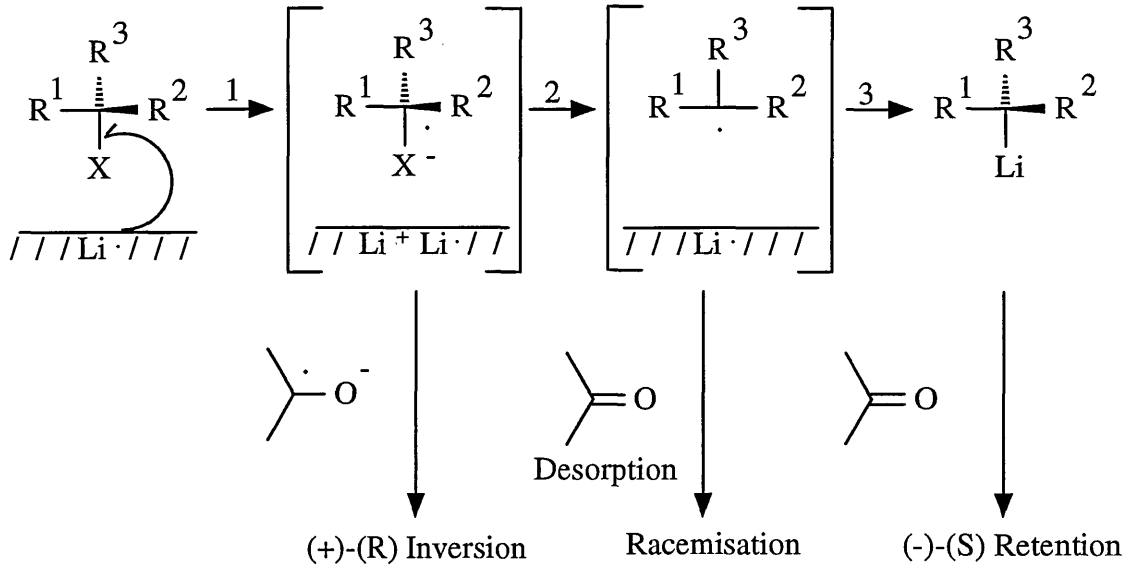


(S)-(+)-2-halooctane

X = Cl, Br, I

(153) (17 -98%)

However at -50 °C it is noted that the absolute configuration is inverted. To explain this effect it is proposed by Luche[311-313] that the Barbier reaction follows a radical pathway [Scheme 120]. Step 1 involves the single electron transfer from the lithium to the carbon-halogen bond. The resultant radical anion can then react with the ketone or ketyl radical anion to produce an inversion of configuration in the alcohol. Alternatively in step 2, the radical anion can lose the halogen atom to form the radical species which can attack the carbonyl compound to form a racemic mixture. This radical formed in the last step can also react with a lithium atom in step 3 to form an organometallic intermediate which will then react with the carbonyl group to retain the configuration.

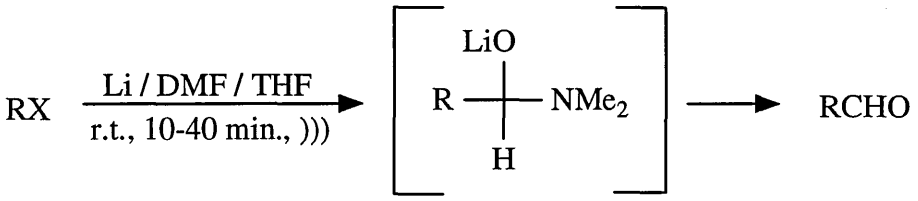


[Scheme 120]

To explain the temperature effect it was proposed[311-313] that ultrasound promoted the SET in the first step, whereas the subsequent steps were ultrasound insensitive but dependent on temperature. Therefore step 1 was promoted at low temperatures and high ultrasonic intensities resulting in an accumulation of the absorbed anion which can then react with the ketyl radical. This results in inversion at the chiral centre to form increased amounts of the (+)-(R) alcohol. The reactivity difference between the halogen compounds is explained by how tightly the ions are adsorbed onto the metal surface. The chloride ion is more tightly adsorbed onto the surface than the other halides, making the chloride ion less reactive toward the ketyl radical explains why a greater proportion of inverted product is observed in the bromoalkyl halide.

Amides

Carbonyl compounds can be synthesised from amides using organometallic reagents. Aldehydes have been produced from formamides although the selectivity is not good in the quiet reaction. When ultrasound is applied[314] the yield is improved and the method can be applied to several halide compounds in DMF [Scheme 121].

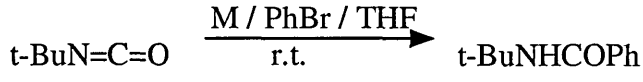


[Scheme 121]

A frequency effect was found when using other amides in diethyl ether. When the reaction was sonicated at 50kHz frequency the reaction was inhibited, but when 500kHz frequency was used[315] the reaction improved. It was proposed therefore that cavitation was not responsible for the chemical effects observed. This conclusion is reached because diethyl ether does not cavitate readily and any increase in frequency will disfavour cavitation.

Magnesium & Sodium in the Barbier Reaction Isocyanates

Although the reaction is sensitive to the metal used in the Barbier type reaction the conversion of isocyanates into amides can be improved by ultrasound significantly. The previous reactions have illustrated how lithium is superior, however in the reaction of t-butyl isocyanate[316] magnesium and sodium give the best yields overall [Scheme 122].



M	Conditions	Time	Yield (%)
Na	Stir	48 h	53
Li	)))	15 min	51
Na	)))	45 min	78
Mg	)))	15 min	91

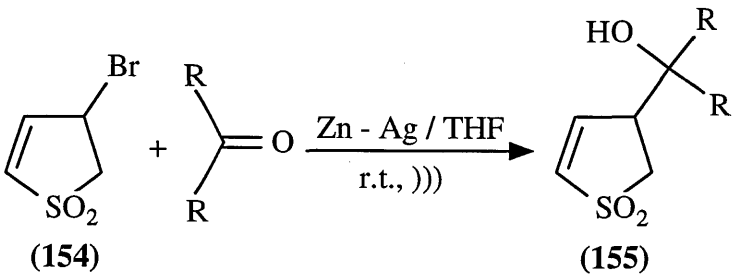
[Scheme 122]

Zinc Metal in the Barbier Reaction

Several reactions in the Barbier type conditions have been investigated using zinc as the metal, which is less reactive and as a result offers the potential for alternative selectivity potential.

Carbonyl Groups

In the presence of a zinc-silver couple[317] aldehydes and ketones react readily with the allylic bromide compound below **(154)** to produce **(155)** in good yield and complete regioselectivity [Scheme 123].

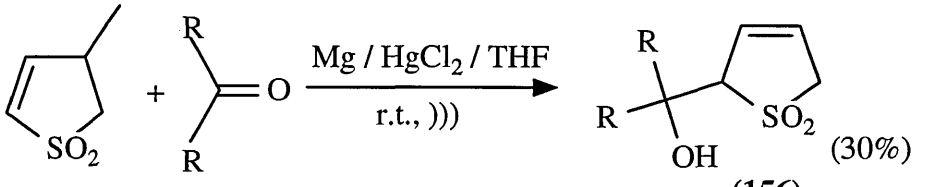


(154) **(155)**

r.t.,))), 4h (78 - 92%) stir, reflux, 12h (33%)

[Scheme 123]

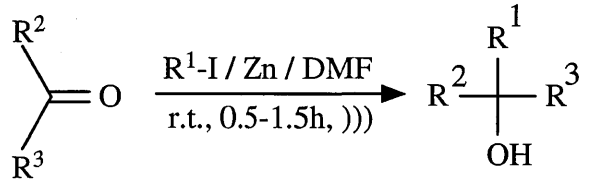
As can be seen sonication increases the yield and reduces the reaction time. When the Zn-Ag is replaced with magnesium and mercury chloride the regioselectivity is reversed with the carbonyl compound adding to the 2-position on the ring **(156)**.



(30%)

(156)

A perfluoroalkyl group can also be added to a carbonyl group. Using DMF as solvent no pre-activation of zinc is necessary to obtain satisfactory yields[318] [Scheme 124].

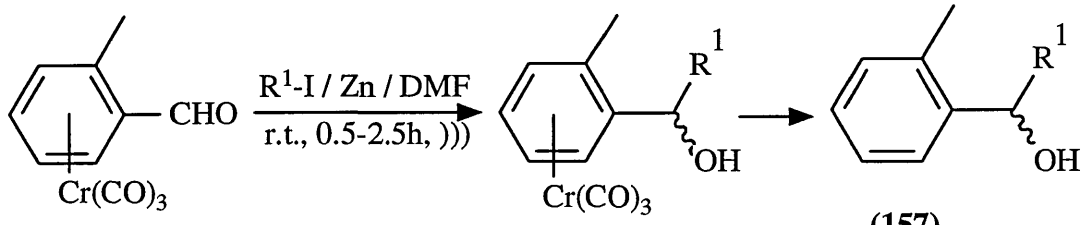


R^1 = perfluoroalkyl R^2 = H , CH_3 R^3 = alkyl, aryl, vinyl

[Scheme 124]

Addition to ketones is poor but this can be improved by catalysis with bis(π-cyclopentadienyl)titanium[282], which is sonochemically prepared from titanocene dichloride by reduction with zinc. Chiral perfluoroalkyl aryl carbinols

(**157**) have been synthesised from a 2-methylbenzaldehyde with a chromium tricarbonyl group attached to the ring [Scheme 125]. The presence of the transition metal group[319] in the precursor is required to provide the chirality.



R^1 = perfluoroalkyl

(157)

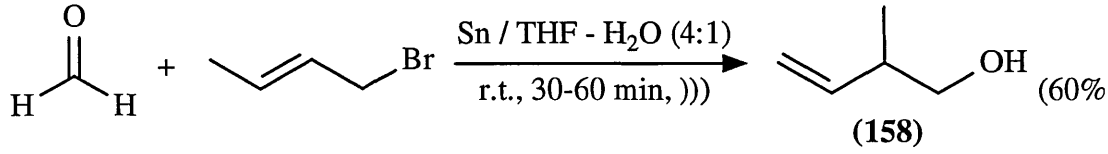
[Scheme 125]

The Barbier-type Reaction with Aqueous Media

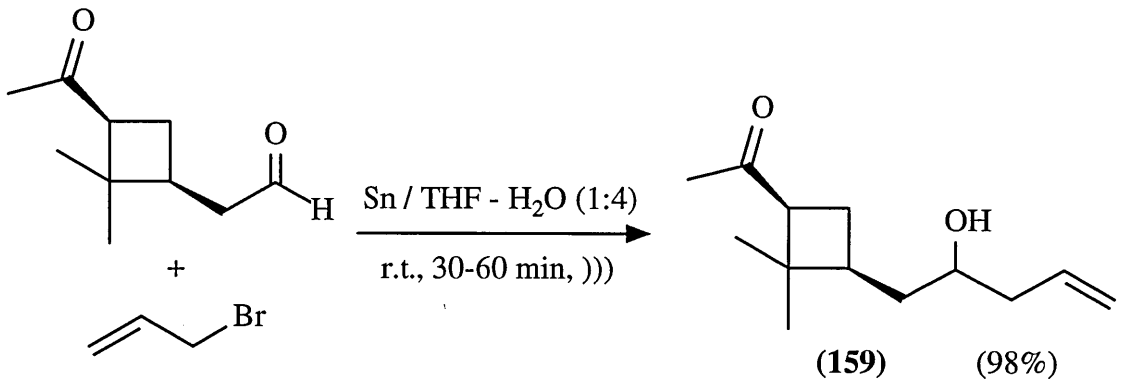
Water in the presence of organometallic reactions is usually strictly avoided because the water will hydrolyse the organometallic reagent when it forms or it will inhibit its formation in the first place. Despite this the following reactions illustrate how water can be used as a co-solvent in this type of reaction.

Carbonyl Compounds

Allylation of carbonyl compounds has been shown to occur with allylic bromides or chlorides in the presence of zinc powder[320] in a 4:1 ratio of THF/H_2O. A poor yield and lengthy reaction time under conventional methods is improved by the application of ultrasound. The zinc can also be replaced with tin[321] to produce compounds **(158)** & **(159)** with moderate to good yields [Scheme 126]. Ketones are found to react slower than aldehydes and a clean monoallylation occurs with bifunctional molecules, which illustrates the method has selectivity. The method has application for starting materials which are insoluble in the more common solvents used for organometallic chemistry, or starting materials that are highly soluble in water[322].



(158)

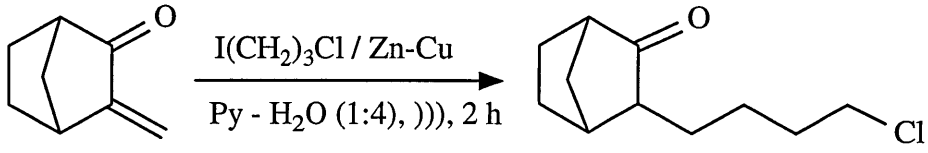


(159) (98%)

[Scheme 126]

α-Unsaturated Carbonyl Compounds

Allylations of α-unsaturated carbonyl groups in aqueous media with zinc or tin selectively occur in a 1,2-addition on the carbonyl carbon. Saturated alkyl halides which are normally unreactive can be made to react in a conjugate 1,4-addition to an α-enone using a zinc-copper couple. This is prepared by sonicating zinc powder and copper iodide in the reaction solvent before adding the reagents[323], which are sonicated further to yield the expected product **(160)**.



(160) (85%)

The halides were found to have a reactivity order as follows : iodides > bromides >> chlorides (unreactive), and tertiary > secondary > primary. It was found that β,β-disubstituted carbonyl compounds react in low yield and that the reaction was sensitive to solvent composition. Ethanol with 10% water was found to promote reaction of secondary and tertiary iodides, whereas primary iodides reacted with mixtures of water and propanol, isopropyl alcohol or t-butyl alcohol. The sound absorption properties of the solvent mixture and the yield showed a correlation[324,325] and can be compared to a previous reaction (the solvolysis of t-butyl chloride in ethanol) which showed a similar effect[90].

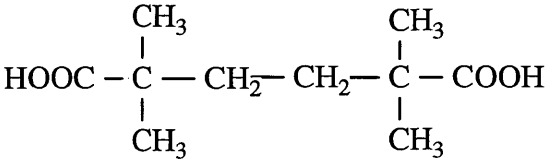
2.0 DISCUSSION

2.0 DISCUSSION AND RESULTS

2.1 DIMERISATION OF PIVALIC ACID USING FENTON'S REAGENT

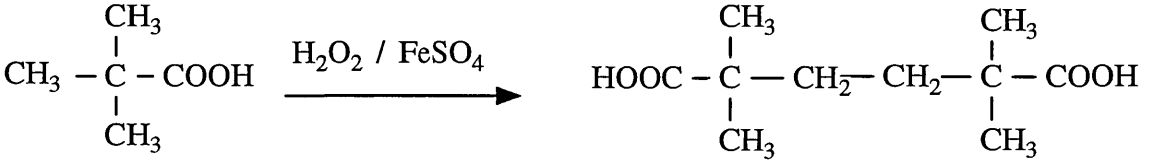
2.1.1 Introduction

Tetramethyladipic acid **(161)** is an important compound produced commercially. It is used in the synthesis of polymeric material on a commercial scale.



(161)

One synthesis of this compound is achieved by the oxidative dimerisation of pivalic acid **(162)** using Fenton's reagent[326].

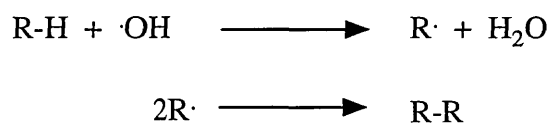


(162) **(161)**

Fenton's reagent[326] combines hydrogen peroxide and a ferrous salt in an aqueous system to generate hydroxyl radicals by a single electron transfer according to the following equation.

Hydroxyl radicals have been used for several applications: initiation of vinyl polymerisations[327], oxidation of acids, alcohols, amines and other organic compounds[328] and in the hydroxylation of aromatic compounds[329] to obtain phenols.

For the purposes of this area of research it has previously been shown[330] that under appropriate conditions of dilution and pH, a wide variety of aliphatic compounds undergo oxidative dimerisation where the hydroxyl radical removes a hydrogen atom bonded to carbon and the alkyl free radicals dimerise [Scheme 127].



[Scheme 127]

The hydrogen atoms do not require activation by a carbonyl group, and the hydrogen atoms of a t-butyl group react readily. Coffman *et al*[330] found that the carbon-hydrogen bond in pivalic acid was three times as sensitive to hydroxyl radical attack as was a carbon-hydrogen bond in acetic acid, i.e. pivalic acid appeared to be about nine times as reactive as acetic acid on a molar basis. This was attributed to α-substitution decreasing the deactivating effect of the carboxyl group. The reaction is non-chain radical and one mole of hydroxyl radical must be generated for each mole of organic reactant consumed.

Previous work[2,173] has shown that sonication of reactions can accelerate radical reactions; it therefore seemed logical that this reaction would benefit from the effects of ultrasonic irradiation. Thus the aim of the initial research was to study the effect of Fenton's reagent on production of TMAA in the presence and absence of ultrasound.

FENTON'S REAGENT

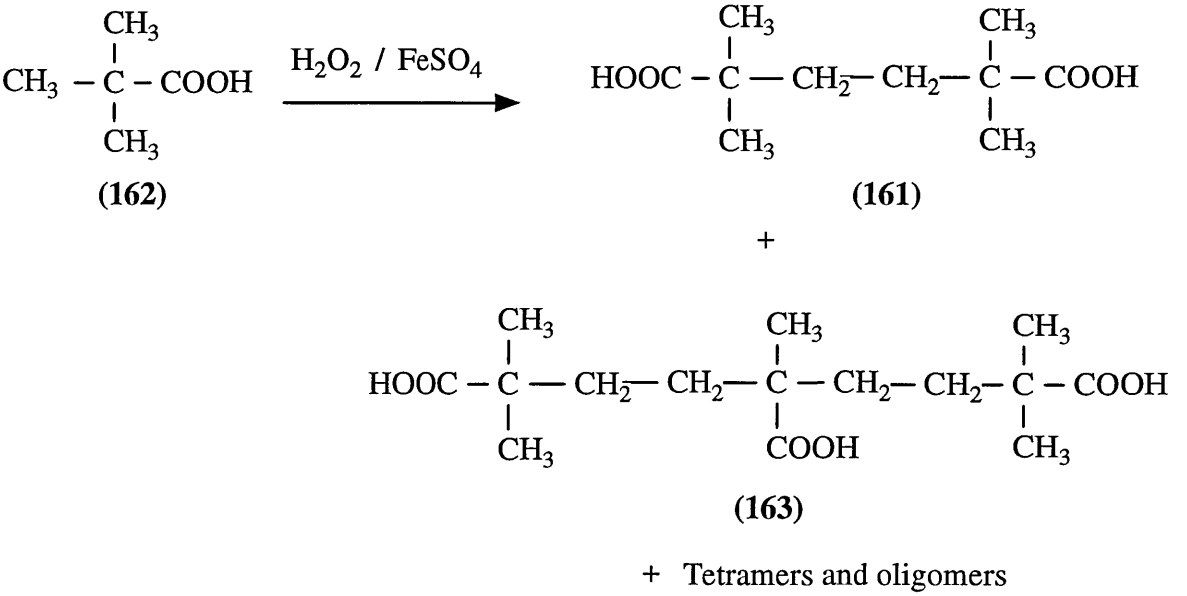
The previous section (2.1.1) discussed how the combination of hydrogen peroxide and ferrous sulphate in acidic, aqueous solution brings about the formation[326] of hydroxyl radicals. The combination of hydrogen peroxide and a ferrous salt is frequently referred to as Fenton's reagent because of his extensive studies[326] with this oxidising system. The hydroxyl radicals produced from Fenton's reagent can abstract hydrogen atoms from certain compounds which results in carbon centred radicals, which then react to form a dimer of the starting material. The coupling is accomplished by simply adding equimolar quantities of hydrogen peroxide and ferrous sulphate to an aqueous solution of the organic reactant.

The applicability of this synthesis is limited by the requirements that the compound to be coupled must be appreciably soluble in an aqueous medium and must not be susceptible to oxidative degradation. Since the attack of hydroxyl radicals on aliphatic compounds is not highly selective, isomeric products are obtained except when symmetrical reactants containing only equivalent hydrogens are used[330]. For example pivalic acid and pivalonitrile give only one isomer of the dimer, whereas, in

contrast, n-butyric acid forms a mixture[330] comprised of at least six of the C_8-dibasic acids. The concentrations of hydroxyl radical and of organic substrate have an effect on yield, as does pH, and rate of addition of the reactants. Therefore conditions for each combination of reaction vessel and starting material have to be optimised[330].

2.1.2 Initial Work

First attempts at dimerising pivalic acid **(162)** under the literature conditions[330] using 2 equivalents of Fenton's reagent produced a reaction mixture that contained three major products (by tlc) as well as some unreacted starting material. Column chromatography of the reaction mixture gave recovered pivalic acid **(162)** (30%), followed by tetramethyladipic acid **(161)** (TMAA) (14%) identified from its spectroscopic data and comparison with literature melting point[330]. The next product eluted was the trimer **(163)** (30%). Analytical figures indicated a formula of $C_{15}H_{26}O_6$ and the proton and carbon nmr spectra were consistent with the structure **(163)** rather than a branched isomer.



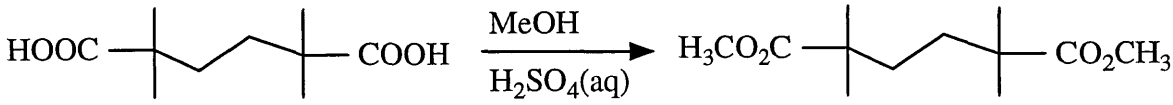
(162) **(161)** + **(163)** + Tetramers and oligomers

[Scheme 128]

The composition of the final material was tentatively assigned to a mixture of tetramers and oligomers (23%). The pmr and cmr spectra were very complex and the mass spectrum showed high molecular weight species present. All yields are reported based on the mass of products obtained and does not take into account recovered pivalic acid.

2.1.2.1 Separation of Oligomers

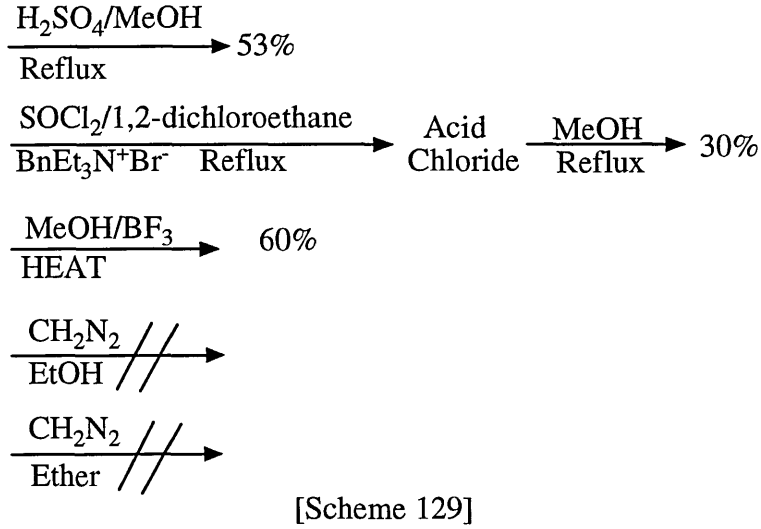
An attempt was made to esterify TMAA to make the polar acid products easier to separate by column chromatography or even gas chromatography. Refluxing TMAA in acidic methanol produced the corresponding diester in 60% yield.



(161) **(164)**

Using this method esterification of the baseline products gave a poor yield (<10%) as did a similar treatment of the reaction mixture (<30%). Therefore, esterification by this method and subsequent analysis is not feasible.

Further attempts were made to esterify isolated TMAA, these are illustrated below:



[Scheme 129]

The failure of diazomethane to esterify the diacid is surprising since this is a standard way to esterify acids. It is thought that only one of the acid groups is esterified, hence the monoacid was lost in work up. Esterification was shown not to be a viable option in the analysis of the products obtained from the dimerisation of pivalic acid and was not continued further.

2.1.2.2 HPLC

An investigation into the possibility of using hplc as a method for obtaining accurate reproducible analysis of the reaction mixture was investigated. The best method obtained is outlined in the experimental section. Unfortunately reproducible results could only be obtained for pivalic acid and its dimer TMAA. In the case of the tetramers this could be due to the fact that they are a complex mixture of isomers and

not a single compound. Another factor could be that the detector had to be operated on a wavelength (217nm) which was at the limit of its detection range. The solvent also absorbed UV to a certain degree at this wavelength.

2.1.2.3 Sonication

It has been suggested by Luche *et al*[173] that ultrasound may be of benefit in certain radical reactions. The fact that the hydrogen peroxide/ferrous sulphate mediated coupling of pivalic acid involves the intermediacy of both hydroxyl and carbon radicals suggested that the use of ultrasound would be helpful in this reaction. It has also been shown that ultrasound can be used to excite oxidising agents such as hydrogen peroxide[85]. When the reaction in Section 2.1.2 was repeated with sonication (power setting 8), which simply involved the immersion of a sonic probe directly into the beaker containing the reaction mixture, the yield of **(161)** increased to 33%, with 30% of starting material recovered; 20% of trimer and 17% tetramers and oligomers also produced. The reaction was also repeated using a high shear stirrer to determine if the ultrasound was simply acting as an efficient stirrer. The yield of TMAA (14%) was not increased over the stirred reaction and the yield (41%) of the side products was not significantly changed either.

Using the knowledge and experience gained in the experiments above, the original experimental work reported in the literature[330] was repeated. In this method a solid product was obtained by filtration from the reaction mixture (36%), and it was assumed by the authors to be the dimer TMAA. However, when the reaction was repeated and the reaction mixture worked up, tlc indicated that the crude product was in fact a mixture of acids which when separated gave TMAA (20%) and mixed isomers (23%), assumed to be the trimers and tetramers discussed above. This result suggests that the yield obtained in the literature method included a mixture of the isomeric acids detailed above. Using a synthetic method supplied by Shell Research produced a similar result, where TMAA (9%) and the associated oligomers (22%) were isolated from the reaction mixture.
Clearly by using different reaction conditions, the yield of TMAA and the oligomers could be altered significantly.

2.1.2.4 Initial Study on the Effect of Number of Equivalents of Fenton's Reagent

In order to ascertain the effect of varying the amount of Fenton's reagent on the yield of both the stirred and sonicated reactions, dimerisation was carried out with 1, 2 and 3 equivalents and the results are shown in Table 2.1.

Yield calculation

One mole of Fenton's reagent should create one mole of the radical generated from pivalic acid. Two of these radicals will then combine to form 0.5 mol of the tetramethyladipic acid. Therefore one mole of Fenton's reagent will form 0.5 mol of TMAA and on this basis the yield was calculated. The yield can be calculated by the conventional method based on mass recovered. However, this method is not applicable in this reaction, since, as the equivalents of Fenton's reagent are reduced the mass recovered becomes very small. Using yields based on Fenton's reagent gives a realistic account of the amount of product (TMAA) formed per mole of reagent used.

Table 2.1

Effect of Molar Equivalents of Fenton's reagent
(TMAA Yield (%) Based on Fentons Reagent)

	SONICATED			STIRRED		
Yield	22	16	8	20	7	2
Equivs	1	2	3	1	2	3

The reactions were carried out over the same time period (30mins) and in the same reaction flask. These results appear to indicate that sonication of the reaction had a positive effect over simply stirring at three different equivalent values of Fenton's reagent. Although the yields decrease with increased amount of reagent, the sonicated reactions have a higher yield than the equivalent stirred reaction.

2.1.2.5 Effect of Temperature

The final temperature reached at the end of the reaction when using ultrasound and 2 equivalents of Fenton's reagent was 67 °C. This high temperature resulted from no external cooling of the reaction vessel. It was not known if this increased temperature

played a role in the low yield of TMAA (16%) that was obtained from this reaction, therefore, the effect on yield by varying the temperature of the reaction was investigated (Table 2.2).

Table 2.2

Effect of Temperature on Yield of TMAA (%)	
Maximum Temperature (°C)	Yield (%)
84	8
67	10
35	16
19	16

It is well known[6] that sonochemical reactions are favoured by lower ambient temperatures as this reduces the possibility of vapour migration into the void created by ultrasound, which reduces cavitation intensity. As expected, when the temperature of reaction was varied, higher yields were obtained at the lower temperatures. However, there is no particular advantage in carrying out the reaction at a temperature lower than 35 °C as the same yield is obtained at 19 °C. All subsequent reactions were carried out by maintaining the temperature of the reaction mixture below 35 °C by immersing the reaction vessel in an ice/water bath.

2.1.2.6 Effect of Ambient Gas

Initially, all the reactions were conducted in an open beaker on a 0.1M scale but since the effect of the gas dissolved in the solvent in sonochemical reactions is known to be important[6], the dimerisation was studied using two equivalents of Fenton's reagent in a specially designed sonochemical reactor vessel at 30 °C (Appendix 1). Using this unit it is possible to seal the vessel and reactions can be studied by ensuring only the gas of interest is admitted. However, the size of the vessel only allowed for reaction at 0.025 molar scale. Table 2.3 shows the yields of TMAA and oligomers obtained for both sonicated and stirred reactions with the appropriate gas was bubbled through the solution of reactants[6,134].

Table 2.3

Effect of Dissolved Gas on Yield of TMAA (%)						
	SONICATED			STIRRED		
	TMAA	OLIG	TOTAL	TMAA	OLIG	TOTAL
AIR	13	13	26	6	20	26
ARGON	9	21	30	6	16	22
NITROGEN	16	11	27	6	16	22

The best yield of TMAA (and also the lowest amount of oligomers) is obtained using ultrasound, with nitrogen gas bubbled through the reaction. Since air is a mixture of gases it is impossible to draw any definite conclusions from this result but the difference in yields between nitrogen and argon is marked. Considering the sonicated results first, it is noteworthy that the total yield of products is approximately the same in each case with the differences lying in the relative ratio of dimer to oligomers. This would appear to indicate that in the presence of nitrogen the hydroxyl radicals have a greater affinity for unreacted pivalic acid, whereas under argon, the favoured reaction is that with TMAA. In the stirred reactions there is generally a much lower yield of TMAA and more oligomers are produced (compared to the sonicated reaction) though the total yield is the highest in the presence of air (due to a very high yield of oligomers). Thus, under these initial conditions with two equivalents of Fenton's reagent it would seem that sonication in the presence of nitrogen gas favours the formation of the dimer while all other conditions produce a greater amount of oligomers.

2.1.3 Follow-up Study: Equivalents of Fenton's Reagent

From table 2.3 it can be seen that the best yields are obtained using nitrogen, so the effect of altering the molar equivalents of Fenton's reagent in the reactor vessel under nitrogen was examined. (Table 2.4).

Table 2.4

Effect of Number of Equivalents on Yield of TMAA(%)				
	Sonicated Yield		Stirred Yield	
Equivs.	TMAA	OLIG	TMAA	OLIG
2	14	11	5	16
1	26	28	11	36
0.5	33	22	34	18
0.33	61	< 5	55	<5
0.167	60	<5	71	<5

Table 2.4 indicates that with both sonication and stirring, low overall yields are obtained with high equivalents and these conditions also lead to oligomer formation. As the number of equivalents is reduced, the formation of oligomers is virtually eliminated since pivalic acid is then in vast excess compared to the number of hydroxyl radicals and so dimerisation is the favoured reaction. Higher equivalents of hydroxyl radicals lead to increased yields of oligomers since pivalic acid is no longer in vast excess. Interestingly, there is little difference in the total combined yield at each equivalent level when the sonicated and stirred reactions are compared but there are considerable differences in product distribution.

2.1.4 Comprehensive Study

After carrying out the experiments described above, the effect of ultrasound on the reaction was studied in greater detail. A number of possible variables such as the blanket gas; equivalents of Fenton's reagent; concentrations of starting materials and/or reagents; ultrasonic power; frequency of ultrasound; pH; addition methodology; ultrasound or mechanical stirring; and terminal reaction temperature may all have an influence on the reaction. After consideration of the initial results and previous work[330] it was decided that the effect of varying the blanket gas, equivalents of Fenton's reagent, dilution and ultrasound or stirring would be studied in depth. In a complex reaction system such as this, a common approach[331] is to first determine which, if any, factors or interactions are important by running an experiment with every combination of each factor at their extreme values, i.e. high and low. A follow up experiment can then be performed varying only these variables

which have been shown to have a pronounced effect in order to determine the optimal combination of factor levels. The data used are a twice replicated 2^3 experiment for each of the three gases, i.e. there are two observations each of every combination of three factors at two levels. The factors used and the data obtained are shown in Table 2.5. Thus, experiments 1 and 2 are the duplicate results for reactions having 0.33 equivalents of Fenton's reagent, low dilution (i.e. most concentrated solution), and ultrasound applied for each of argon, oxygen and nitrogen being bubbled through the solution.

Table 2.6 gives the analysis of variance for the whole experiment and tables 2.7, 2.8 and 2.9 consider the individual gases.

Table 2.5 Factors and Data for Effect on Yield

				% of TMAA		
Exper. No.	Equiv.	Dil.	US.	Ar	O_2	N_2
1	0.33	low	on	54	33	63
2	0.33	low	on	54	36	60
3	0.17	low	on	48	21	76
4	0.17	low	on	45	19	71
5	0.33	high	on	37	26	64
6	0.33	high	on	33	26	57
7	0.17	high	on	57	29	67
8	0.17	high	on	57	24	67
9	0.33	low	off	60	29	60
10	0.33	low	off	55	32	67
11	0.17	low	off	64	47	80
12	0.17	low	off	67	51	83
13	0.33	high	off	57	45	74
14	0.33	high	off	60	43	67
15	0.17	high	off	40	0	81
16	0.17	high	off	36	0	86

Table 2.6 Analysis of Variance for Yield for Whole Experiment.

Source	DF	SS	MS	F	P
eq	1	12.00	12.00	1.57	0.222
dil	1	420.08	420.08	55.09	<0.0005
ultra	1	533.33	533.33	69.95	<0.0005
gas	2	13737.8	6868.9	900.84	<0.0005
eq*dil	1	270.75	270.75	35.51	<0.0005
eq*us	1	56.33	56.33	7.39	0.012
eq*gas	2	991.62	495.81	65.02	<0.0005
dil*us	1	102.08	102.08	13.39	0.001
dil*gas	2	238.29	119.15	15.63	<0.0005
us*gas	2	50.04	25.02	3.28	0.055
eq*dil*us	1	1518.75	1518.75	199.18	<0.0005
eq*dil*gas	2	321.13	160.56	21.06	<0.0005
eq*us*gas	2	198.04	99.02	12.99	<0.0005
dil*us*gas	2	327.54	163.77	21.48	<0.0005
eq*dil*us*gas	2	823.88	411.94	54.02	<0.0005
Error	24	183.00	7.63		
Total	47	19784.67			

Table 2.7 Analysis of Variance for Argon.

Source	DF	SS	MS	F	P
eq	1	1.00	1.00	0.19	0.674
dil	1	306.25	306.25	58.33	<0.0005
us	1	182.25	182.25	34.71	<0.0005
eq*dil	1	0.25	0.25	0.05	0.833
eq*us	1	182.25	182.25	34.71	<0.0005
dil*us	1	81.00	81.00	15.43	0.004
eq*dil*us	1	841.00	841.00	160.19	<0.0005
Error	8	42.00	5.25		
Total	15	1636.00			

The average yields for each combination is;

		Equivalents	
		0.33	0.17
Dil low	US on	54	35
	US off	57.5	58.5
Dil high	US on	46.5	57
	US off	65.5	38

Table 2.8 Analysis of Variance for Oxygen.

Source	DF	SS	MS	F	P
eq	1	390.06	390.06	93.15	<0.0005
di	1	351.56	351.56	83.96	<0.0005
us	1	68.06	68.06	16.25	0.004
eq*dil	1	564.06	564.06	134.70	<0.0005
eq*us	1	33.06	33.06	7.90	0.023
di*us	1	280.56	280.56	67.00	<0.0005
eq*dil*us	1	1501.56	1501.56	358.58	<0.0005
Error	8	33.50	4.19		
Total	15	3222.24			

The average yield for each combination are:

		Equivalents	
		0.33	0.17
Dil low	US on	34.5	20.0
	US off	30.5	49.0
Dil high	US on	26.0	26.5
	US off	44.0	0.00

Table 2.9 Analysis of Variance for Nitrogen

Source	DF	SS	MS	F	P
eq	1	612.56	612.56	45.59	<0.0005
di	1	0.56	0.56	0.04	0.843
us	1	333.06	333.06	24.79	<0.0005
eq*di	1	27.56	27.56	2.05	0.190
eq*us	1	39.06	39.06	2.91	0.127
di*us	1	68.06	68.06	5.07	0.055
eq*di*us	1	0.06	0.06	0.00	0.947
Error	8	107.50	13.44		
Total	15	1188.44			

The average yields for each equivalent / ultrasound combination are:

	Equivalents	
	0.33	0.17
Us on	61.0	70.3
Us off	67.0	82.5

The optimal combination of variables for the production of TMAA is 0.17 equivalents of Fenton's reagent under nitrogen and no ultrasound. The yields were 81.5% and 83.5% respectively at low dilution and high dilution.

Gases

Table 2.6 shows the analysis of variance for the whole experiment and significant differences in the yield for the three gases can readily be seen. More importantly, the value of p <0.0005 for eq*dil*us*gas indicates a significant four factor interaction. (Any factor or interaction with a p value less than 0.05 is usually regarded as significantly affecting the yield). Consequently, the results for each gas were analysed separately (Tables 2.7, 2.8 and 2.9). For argon (Table 2.7) the large three way interaction effect, p <0.0005, shows that, for this gas, the effects of each factor are interdependent. However the effect of changing the equivalents from 0.333 to 0.167 is not significant, (p=0.674), and dilution is not significant (p=0.833). All other effects are significant as seen from the values of p<0.004.

From the average yield for each combination (Table 2.5, entries 11 and 12) it can be seen that the highest average value is 65.5% indicating that for argon the optimal combination is 0.17 equivalents, low dilution, with no ultrasound.

Applying the same arguments to the results for oxygen (Table 2.8), we see that there is a large three way interaction, $p < 0.0005$, indicating that the effect of one factor will depend on the particular combination of the other two. For example, ultrasound has a beneficial effect on yield at high dilution/high equivalents but a detrimental effect at high dilution/low equivalents. No product was isolated when stirring alone was applied at high dilution/low equivalents. The great variety of results and significance of each factor makes this gas impossible to analyse. This is probably a reflection on the fact that oxygen is known to greatly influence reactions involving radicals[332,333] and there are many cases[6] where yields from sonochemical reactions are greatly reduced in the presence of this gas. From the values of the means for each combination it can be seen that the optimum level is 0.167 equivalents, low dilution and no ultrasound but on average the yield obtained with oxygen is the lowest of the three gases studied.

For nitrogen (Table2.9) the values of $p < 0.0005$ for both equivalents and the presence or absence of ultrasound shows that only these factors have a significant effect on yield. From the average yield values it can be seen that the optimum combination for nitrogen is at 0.167 equivalents and no ultrasound. The values of low and high dilution were 81.5% and 83.5% respectively indicating that this had no significant effect on the yield. It was discussed in Section 1.3 that the effect of dissolved gases on cavitation is a complex matter, involving the polytropic ratio, gas solubility, and gas type i.e. monatomic or diatomic.

2.1.5 Extended Study

The results from analysis of Table 2.9 indicated that in order to determine fully the optimal conditions for nitrogen gas, a number of additional data points were required and these are shown in Table 2.10.

Table 2.10 Extended Study

Row	Equiv.	Yield	Ave	Mass %
1	0.080	98	98	8
2	0.080	98		
3	0.167	90	87	15
4	0.167	84*		
5	0.200	84	80	15
6	0.220	76		
7	0.240	73	70	17
8	0.240	66		
9	0.280	68	69	19
10	0.280	71		
11	0.330	64	67	21
12	0.330	71*		

* Includes average value from Table 2.5

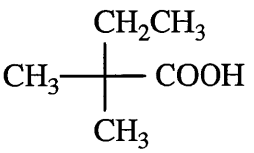
This study utilised the recommendations made from the first set of results which showed that the optimum yields were obtained when the reaction was stirred only, with high dilution, and nitrogen was used as the blanket gas. In addition it was seen that the yield depends on the number of equivalents of Fenton's reagent used. Table 2.10 indicates that the best yield is obtained with the lowest number of equivalents of Fenton's reagent and approaches 100%. However, the mass of TMAA obtained at this level is only 8% (based on isolated product) and so most of the pivalic acid needs to be recycled in order to make this a feasible route to TMAA. Thus, a decision on the relative merits of the high yield based on Fenton's reagent and mass of product isolated needs to be made and in an industrial process this would depend on the relative costs of reagents versus processing costs.

2.1.6 Conclusions

This study shows that the yield depends greatly on the gas being used. For argon and oxygen the optimal combination is 0.17 equivalents of Fenton's reagent, low dilution, no ultrasound. For nitrogen, the optimal combination is 0.17 equivalents of Fenton's reagent, high dilution and no ultrasound. An extension of this study has shown that even further dilution results in higher yields with respect to Fenton's reagent albeit at the expense of the mass of product obtained. Ultrasound does not appear to increase the yields over that obtained with stirring alone. This effect has also been noted[92] in the Diels-Alder reaction of cyclopentadiene and acetamidoacrylates when aqueous solvent is used.

2.1.7 Other Dimerisation Experiments Utilising Fenton's Reagent.

Samples of versatic-6 acid (2,2-dimethylbutanoic acid) **(165)**, and versatic-7 acid ("pitchfork" acid) (2-ethyl-2-methylbutanoic acid) **(166)** that were supplied by Shell Research, were reacted with Fenton's reagent. The reason behind using these compounds was the fact they are very similar to pivalic acid, except the methyl groups are not equivalent. The reaction of these compounds with Fenton's reagent would show if all the methyl groups had to be identical for the successful synthesis of one dimer i.e. would one of the methyl groups in the versatic-6 or versatic-7 acid react preferentially over the other two.



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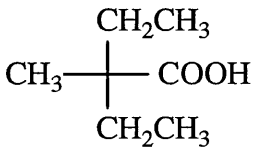


(166)

Versatic 6 acid was reacted with one molar equivalent of Fenton's reagent without ultrasound (with and without phase transfer catalyst). At the end of the reaction only starting material was present. Sonication of the same reaction produced recovered starting material (30%), a mixed fraction (26%) of what was assumed to be the dimer of versatic 6 acid, and a mixed fraction (28%) of other products which were assumed to be a mixture of several possible trimers and tetramers. The analysis of the dimers, trimers and tetramers proved difficult. The compounds were very insoluble and the resulting spectra complex. It is assumed that the products are a complex mixture of all the oligomers possible. It is believed that the stirred reaction does not afford any

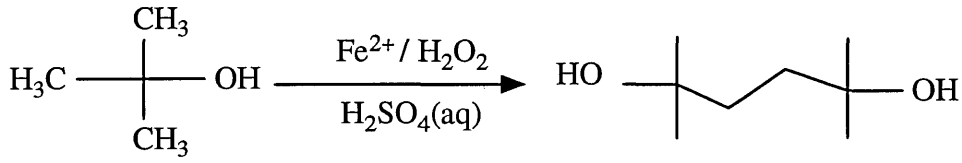
products because of the starting material being insoluble in the aqueous phase. Ultrasound probably enhances the reaction because of its mass transport effect, homogenising the liquid / liquid heterogeneous system.

Versatic 7 acid was reacted with one molar equivalent of Fenton's reagent with sonication. Separation using column chromatography afforded recovered starting material (49%), "B" (12%), and a mixed fraction B/C/D (37%). A repeat of the above reaction afforded recovered starting material (39%), "B" (11%), "C" (6%), "D" (26%).

As with versatic 6 acid, analysis of the products proved difficult because they were insoluble in nmr deuterated solvents and produced complex spectra that were difficult to interpret. From limited spectral data it is believed they are a mixture of all the possible structural isomers of the trimers and tetramers. There are insignificant differences between the results of the stirred and sonicated reactions.

Versatic 6 & 7 acid both produce a highly complex mixture of isomers due to their additional alkyl nature (c.f. pivalic acid). The additional $-CH_2-$ in the structure of these acids can react with the hydroxyl radicals. This is done at the expense of the terminal $-CH_3$ carbon. This increases the chance of product isomerisation. The low yields obtained for these two reactions is due to their low solubility in the aqueous phase, which is a necessary requisite for reaction with Fenton's reagent[330].

It has been reported that t-butanol dimerises with Fenton's reagent[334], to yield 1,1,4,4-tetramethylbutan-1,4-diol **(167)**.



(167)

In this reaction the t-butanol was in excess and a yield of around 50% (based on peroxide used) was reported in the paper. When this experiment was repeated a similar result was obtained. Sonicating this reaction had no measurable effect on the final yield. The lack of effect of ultrasound can be understood when the yield calculation is scrutinised more closely. The authors calculate the yield from the amount of peroxide that is used i.e. one mole of peroxide should produce one mole of dimer, this is not so. One mole of peroxide would produce one mole of hydroxyl

radicals which would react with the t-butanol to give one mole of carbon centred radicals. Therefore when these radicals combined the maximum amount of dimer that could be produced is only 0.5 moles. Therefore, the yield from this reaction is closer to 100% which is impossible to improve on.

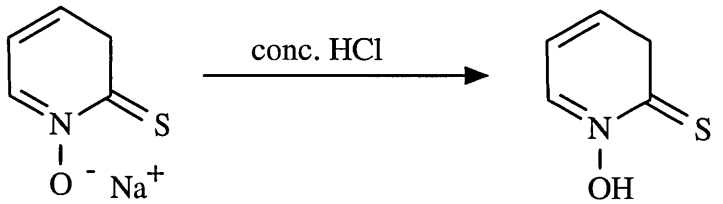
Miscellaneous

As discussed above, ultrasound is well known for its capability for producing radicals within solution. In an attempt to utilise this phenomenon, pivalic acid was sonicated (using a sonic probe as well as an ultrasonic cleaning bath) with water only in the belief that any radicals produced would react with the pivalic acid to produce a carbon centred radical which would, in turn, dimerise to form TMAA. This experiment, however, proved unsuccessful with no TMAA being observed on tlc. Using the same concept pivalic acid, hydrogen peroxide and water were sonicated with the ultrasonic probe. Unfortunately, this reaction did not produce any TMAA. It is thought that any radicals or dimer produced is done so on a microscale that is not apparent on tlc. This renders the experiment useless for synthetic use, and thus is in agreement with previous work[67,335].

2.2 SONICATION OF N-HYDROXYPYRIDINE-2-THIONE

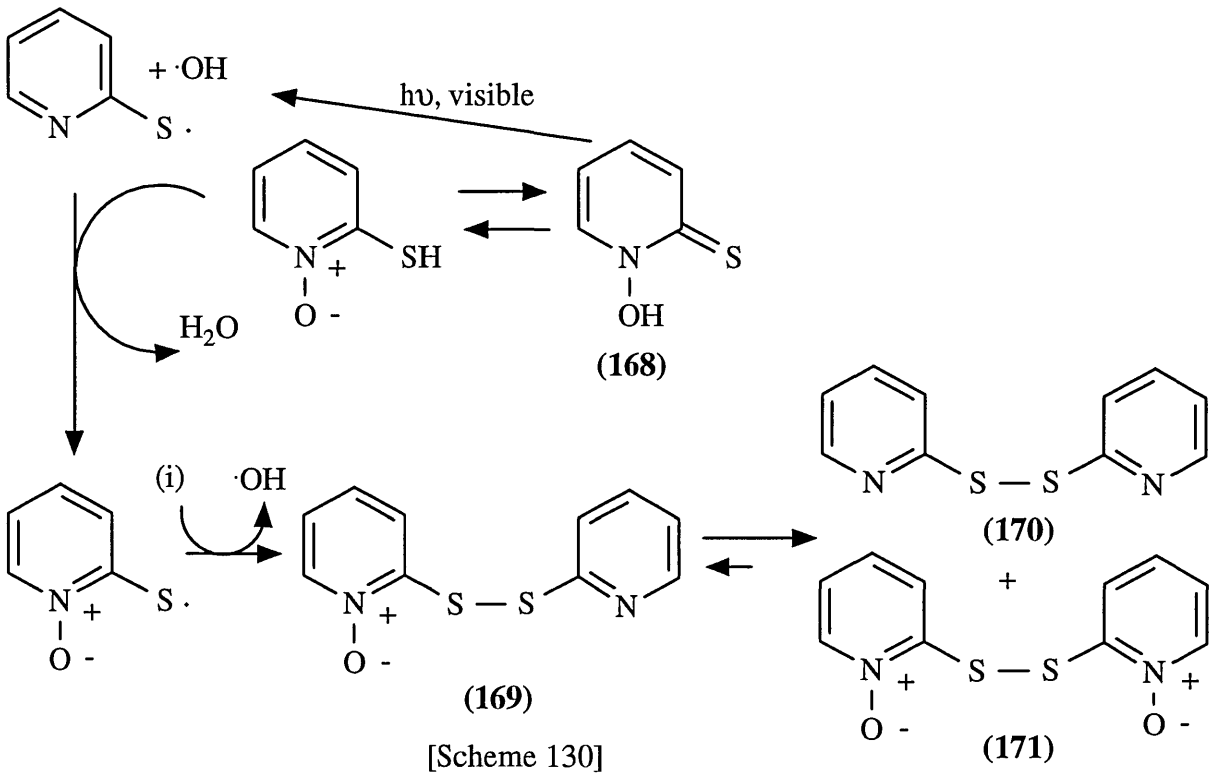
Using Fenton's reagent as a source of hydroxyl radicals is not without its limitations. One of the main problems with the method is that the starting material has to have at least some solubility in water. This is obviously a disadvantage for organic materials, and producing hydroxyl radicals by an alternative route would also complement the work on Fenton's reagent, i.e. production of hydroxyl radicals could be used to dimerise pivalic acid. Therefore, a source of radicals was sought that could be used in an organic solvent and provide a wider scope for radical reactions on a synthetic scale.

Barton and co-workers have shown that the derivatives of N-hydroxypyridine-2-thione **(168)** can be used as precursors of oxygen[336], and carbon[337] centred radicals. This process is initiated by visible light or by heating with or without a radical initiator. It therefore seemed reasonable to expect ultrasound to be an efficient initiator of such radical processes. If ultrasound could be used to initiate radicals from N-hydroxypyridine-2-thione (NHPT) in organic solution it would prove to be a very useful synthetic tool.
NHPT is produced on a large scale as an anti-fungal, anti-dandruff, and antimicrobial additive in many commercial applications[337]. NHPT is supplied as a 40% aqueous solution of its sodium salt, which is treated with concentrated hydrochloric acid to precipitate the solid product[337].



(168)

Boivin *et al*[338] have studied the decomposition of NHPT by irradiating a benzene solution of the compound with visible light (500W, tungsten lamp) for 3 hours. After this time a mixture of monoxide **(169)** (48%), dipyridyl disulphide **(170)** (30%), and dioxide **(171)** (18%) was produced. The mechanism was thought to proceed through radical intermediates as outlined below [Scheme 130].



[Scheme 130]

Initiated by photolysis, NHPT is converted *via* radical intermediates into the monoxide **(169)** which can then disproportionate into the dipyridyl disulphide **(170)** and the dioxide **(171)**. This reaction scheme illustrates that the generation of hydroxyl radicals can be achieved under these mild conditions. The authors exploited the production of hydroxyl radicals by successfully synthesising derivatives of NHPT with isopropanol, THF, 1,3-dioxolane, 1,4-dioxolane, and 1-phenylcyclohexene. It was hoped that the production of these hydroxyl radicals could be used to dimerise pivalic acid or at least produce a derivative of it when it was reacted with NHPT.

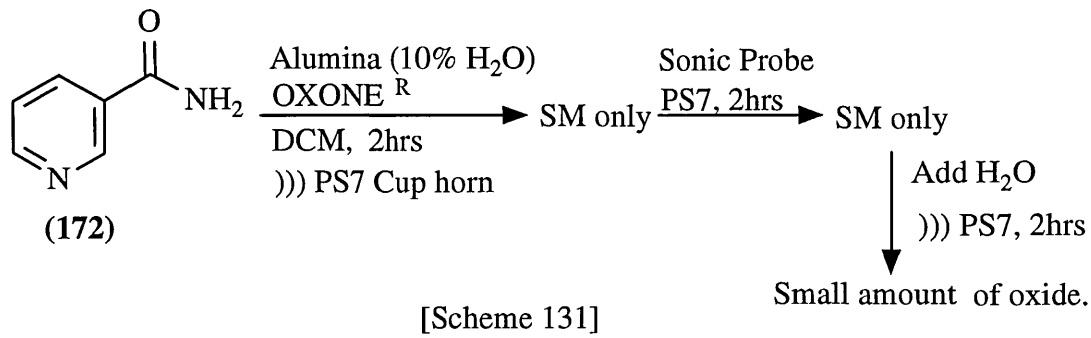
As a starting point an attempt was made to repeat the literature reaction[338], where a benzene solution of NHPT was irradiated with light (500W bulb) for three hours. Tlc indicated a mixture of products which was assumed to be that outlined in the above paper. The reaction with NHPT was then repeated where the reaction vessel was wrapped with aluminium foil to exclude all light. The benzene solution of NHPT was then sonicated with the sonic probe (power setting 5) for 3 hours. After work up, tlc indicated that starting material only was present. In an attempt to increase the amount of cavitation energy introduced into the reaction, various alternative solvents were used (benzene, THF, and ethylene glycol dimethyl ether). Unfortunately, tlc again indicated no product other than starting material was present at the end of the sonication. Benzoyl peroxide was also used in an attempt to initiate the radical

reaction. Again no compounds other than starting material were evident after 3 hours sonication. Another unsuccessful attempt at initiating the reaction involved increasing the ultrasonic intensity (power setting 8). Therefore, considering the various conditions that were attempted, the initiation of the radical reactions from NHPT appear to be light sensitive and not susceptible to ultrasonic irradiation.

As a final reaction with NHPT, a benzene solution of NHPT and pivalic acid were stirred whilst irradiating the solution with light as before. Unfortunately no derivative of pivalic acid was evident from tlc. Since the aim of this section was to investigate alternative sources of HO· and ultrasound was not found to be beneficial, this line of research was not continued further.

2.3 NICOTINAMIDE N-OXIDATION

A number of synthetic routes to N-oxides of pyridines have been reported[339-341]. Recently R.P. Greenhalgh[342] described the use of oxone^R on alumina as a method for oxidation of sulphides to sulphoxides and sulphones. When this reagent was investigated as a method of N-oxidation of nicotinamide **(172)** it was found to proceed to a maximum yield of 50%. Considering the heterogeneous nature of the catalyst in this reaction and the known benefits that ultrasound has in such systems[2], this reaction was sonicated in an effort to increase the yield. Initially nicotinamide, oxone^R, and damp alumina (10%H_2O, w/w) were sonicated in dichloromethane in the sonic cup horn (power setting 7) at room temperature for 2 hours. No reaction occurred (tlc), therefore the reaction flask was removed from the sonic cup horn and the sonic probe was immersed in the reaction mixture, which was sonicated (power setting 7) for a further 2 hours at 35 °C. Once more no oxidation was observed. The wet alumina that had been used was prepared several weeks previously, therefore a small amount of water was added to the reaction mixture in case the alumina had dried out. When this reaction mixture was sonicated for a further 2 hours it was found that a small amount of the N-oxide had formed [Scheme 131].

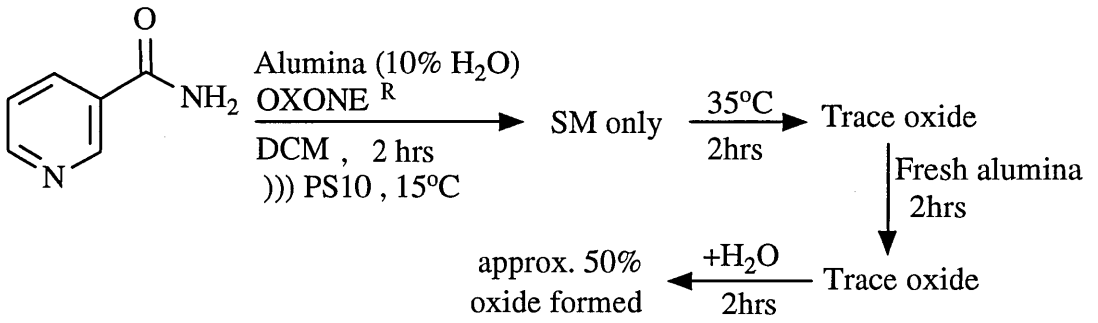


[Scheme 131]

The above reaction was sonicated with the sonic probe (power setting 7) for 90 minutes with fresh, wet alumina and again this produced only a trace of the oxide.

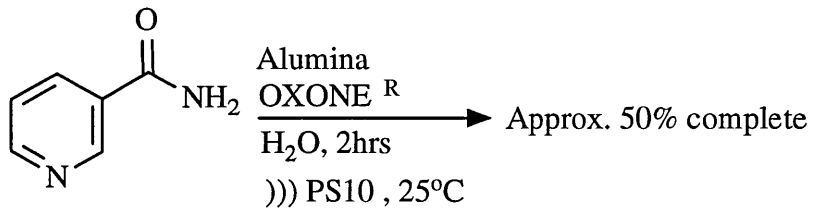
At the third attempt to produce the oxide the ultrasonic intensity was increased (power setting 10) and temperature maintained at 15 °C for 2 hours, no reaction occurred. When the reaction was run for a further 2 hours at 35 °C, oxide was seen to be present in trace amounts, adding fresh alumina and continuing the reaction for a further 2 hours did not improve the yield. However, it was found that if water was added to this reaction the oxide formed readily (approx. 50%). Why the reaction proceeds with an excess of water present is not known. It could be due to a chemical

effect, or that an increase in water content increases the amount of cavitation energy transferred into the reaction.

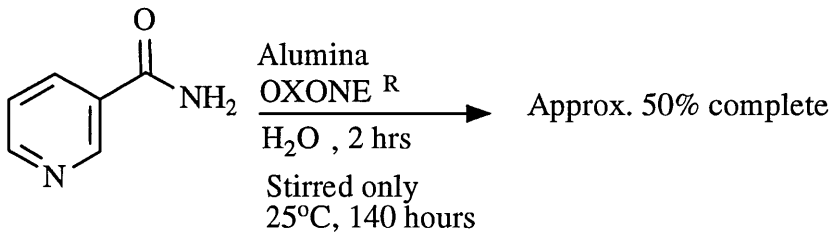


[Scheme 132]

Consequently the reaction was repeated using water as the solvent instead of dichloromethane and after 2 hrs, oxide had formed (approx. 50%) which is still no improvement in yield over the refluxed reaction.



When these conditions were repeated with stirring and no ultrasound, the same level of oxide was only obtained after 140 hrs of stirring.

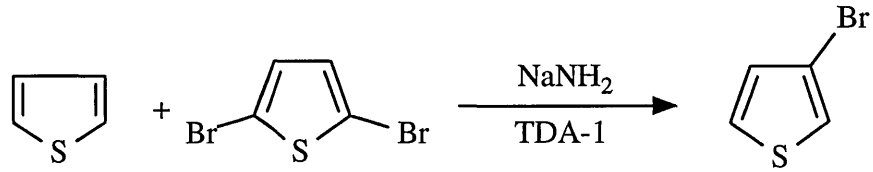


This reaction does illustrate the rate enhancing properties of ultrasound. However, no overall improvement in yield was obtained compared to the previous work in this area, therefore, this reaction was not investigated further.

2.4 PREPARATION OF 3-BROMOTHIOPHENE.

2.4.1 Rearrangement of 2,5-Dibromothiophene to 3BT.

In the agrochemical and pharmaceutical industries, 3-bromothiophene (3BT) is used as a key intermediate in the synthesis of fine chemicals. It was initially produced at Synthetic Chemicals Limited[343,344] by brominating thiophene to 2,3,5-tribromothiophene with bromide/bromate/sulphuric acid in aqueous suspension, then debrominating to 3BT with zinc/acetic acid. This method affords the product in high yield but the cost of adding the bromine atoms then removing them is high, therefore an alternative method was sought. Previous work has shown the possibility for the preparation of 3BT from a low temperature rearrangement of 2,5-dibromothiophene (25DBT) and thiophene in liquid ammonia with sodium iron (III) nitrate (which forms sodamide)[345]. However this method is very limited on a commercial scale since liquid ammonia is difficult to handle. Hoescht has developed a method[346] in which 2-halothiophenes are isomerised to the 3-isomers at 200-250°C over an alumina catalyst, but the two isomers have to be separated at the end of the reaction which is a difficult process[346]. Therefore, at SCL, a method was developed which produced 3BT in good yield and good selectivity[343,347]. Production of 3-bromothiophene involved rearranging 2,5-dibromothiophene using sodamide (3 equivalents). These reagents were stirred in thiophene at 55 °C with a phase transfer catalyst (TDA-1),for 6 hours under nitrogen. After steam distilling the organics out of the reaction mixture this reaction produces a good yield (>80%) with good selectivity (typically a 3BT:2BT ratio of 98:2). An unfortunate side product of this preparation is the formation of a significant amount of pitch.



The principle of applying ultrasound to this reaction was to improve the selectivity towards 3-bromothiophene and/or to reduce the amount of pitch produced.

As a starting point the standard reaction detailed above was repeated (Table 2.11, reaction a) and the expected yield (80%) and selectivity (98:2) of 3-bromothiophene was obtained. This reaction was then carried out while sonicating the reaction mixture (Table 2.11, reaction b) with the sonic probe at power setting 5. The reaction was continued for two hours and after work-up gave a modest yield of 3BT (58%) and

reasonable selectivity (91:9). However, this yield and selectivity were not as high as the quiet standard reaction, therefore the reaction with ultrasound was repeated (Table 2.11, reaction c) over a longer time span (4 hours). This resulted in a better yield (69%) and selectivity (99:1) compared with the 2 hour reaction, but again the standard reaction was not improved upon. It was decided to increase the ultrasound intensity in an attempt to increase the reaction rate. The reaction was sonicated at power setting 7.5 for two hours (yield 78%, selectivity 97:3) (Table 2.11, reaction j), and at power setting 10 for two hours (yield 82%, selectivity 98:2) (Table 2.11, reaction k). This gave more encouraging results. Indeed these conditions gave a yield and selectivity within 2 hours comparable to the stirred equivalent which takes 6 hours to complete. The effect of ultrasound is often enhanced at lower temperature[6] and hence the reaction was carried out at 25 °C and 0 °C with and without ultrasound for 2 hours and 4 hours. When the reaction was sonicated (power setting 5) for 2 hours at 25 °C (Table 2.11, reaction d) the yield and selectivity were reduced significantly (30%, 62:38) and were not improved by increasing the reaction time to 4 hours (32%, 67:33) (Table 2.11, reaction e). These yields were far better than the stirred equivalent where there was practically no reaction (0.76%, 16:84) (Table 2.11, reaction f). A similar trend was found when the reaction was sonicated (power setting 5) for 2 hours at 0 °C (Table 2.11, reaction g). The yield and selectivity were reduced even further (10.5%, 31:69) which did not improve significantly by extending the reaction time to 4 hours (12.4%, 34:66) (Table 2.11, reaction h). There was no reaction at all when the reaction mixture was stirred at 0 °C for 4 hours (Table 2.11, reaction i). Therefore, at temperatures of 25 °C or below the reaction only proceeds when it is sonicated. However there is no advantage in using these conditions when the reaction rate, yield, and selectivity are considered.

It is well known that the surface scouring and mass transport properties of ultrasound can remove passivated layers from the surface of solid reagents, and can also increase reaction rate by increasing the surface area of the reagent by fragmenting the solid into smaller pieces (Section 1.3.3). These effects were used to "regenerate" old sodamide in the above reaction. When a sample of aged sodamide (it was yellow and smelled strongly of ammonia) was used in the standard quiet reaction detailed above, little reaction occurred (1.1%, 7:93) (Table 2.11, reaction l). When the same sodamide was used in a reaction which was sonicated (power setting 5) over a 2 hour period the yield was improved dramatically (69%, 94:6) (Table 2.11, reaction m). This could mean regeneration of old reagents in the laboratory using ultrasound is possible, but this is unlikely on a production scale since commercial companies would

be unlikely to use such a reagent. Again utilising the mass transport properties of ultrasound the phase transfer catalyst (TDA-1) was omitted from the sonicated reaction (power setting 5, 2 hours) (Table 2.11, reaction n) and a reasonable yield and selectivity were still obtained (65%, 87:13).

Table 2.11 Rearrangement of 2-5-dibromothiophene

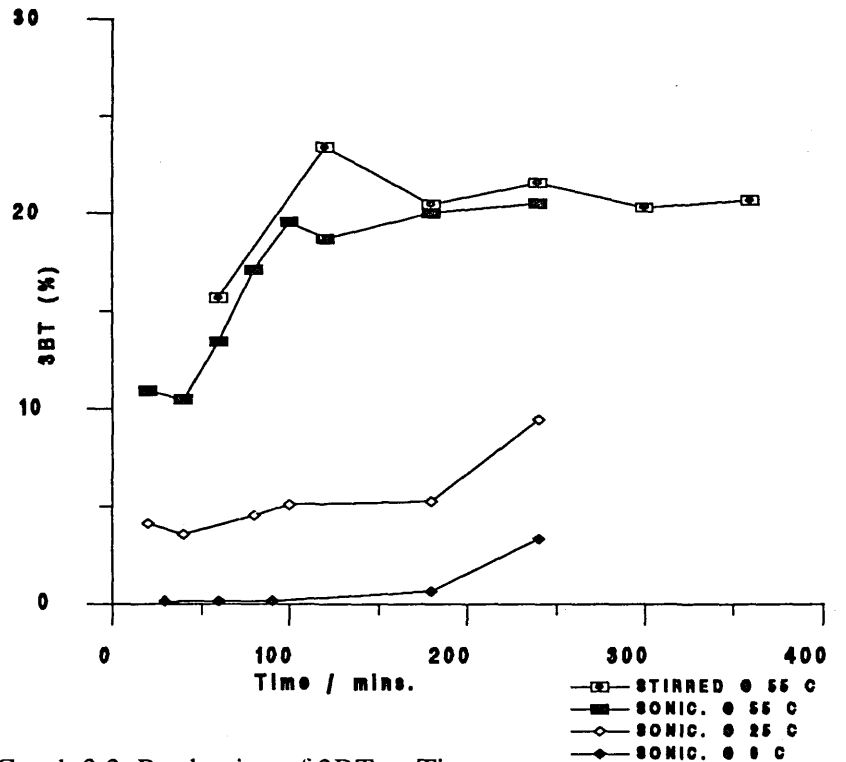
CONDITIONS				3BT(%)	3BT:2BT
a)	Std. reaction			>80	98:2*
b)	))) PS5,	2hrs		58	91:9
c)	))) PS5,	4hrs		69	99:1*
d)	))) PS5,	2hrs,	25°C	30	62:38
e)	))) PS5,	4hrs,	25°C	32	67:33*
f)	Stirred	4hrs,	25°C	0.76	16:84
g)	))) PS5,	2hrs,	0°C	10.5	31:69
h)	))) PS5,	4hrs,	0°C	12.4	34:66*
i)	Stirred,	4hrs,	0°C	0.0	-
j)	))) PS7.5	2hrs,		78	97:3
k)	))) PS10	2hrs,		82	98:2
l)	Old sodamide, stir	6hrs		1.1	7:93
m)	Old sodamide,))) PS5,	2hrs		69	94:6
n)	))) PS5, NO TDA-1	2hrs		65	87:13

* These reactions were sampled throughout for a kinetic study (see graphs),
)))= Ultrasound, PS= Power setting.

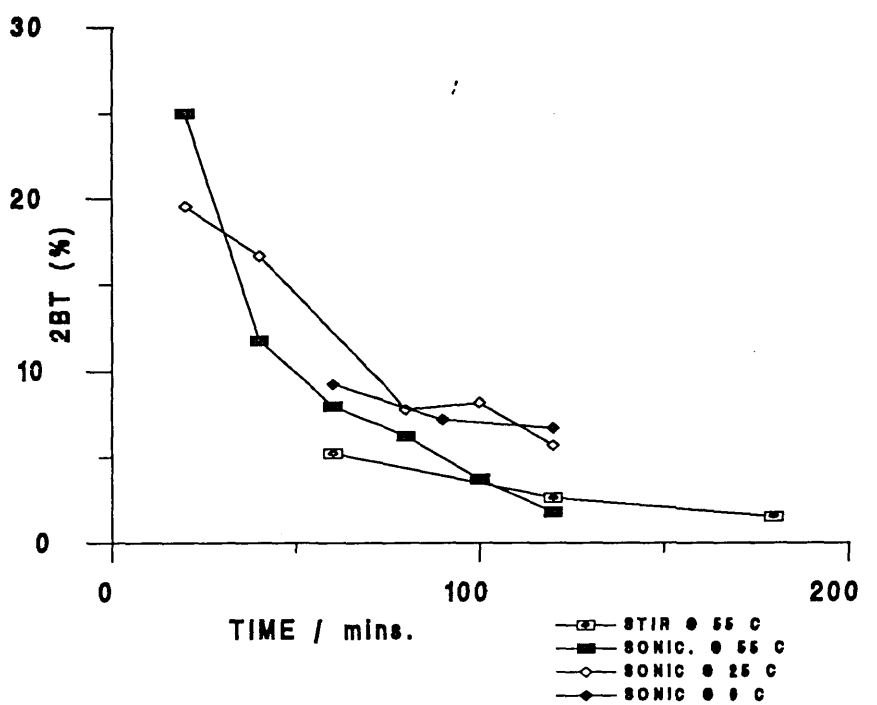
Kinetics

As mentioned above, the reactions marked with an asterisk were sampled throughout to provide a picture of the kinetics.

Graph 2.1 Production of 3BT vs Time

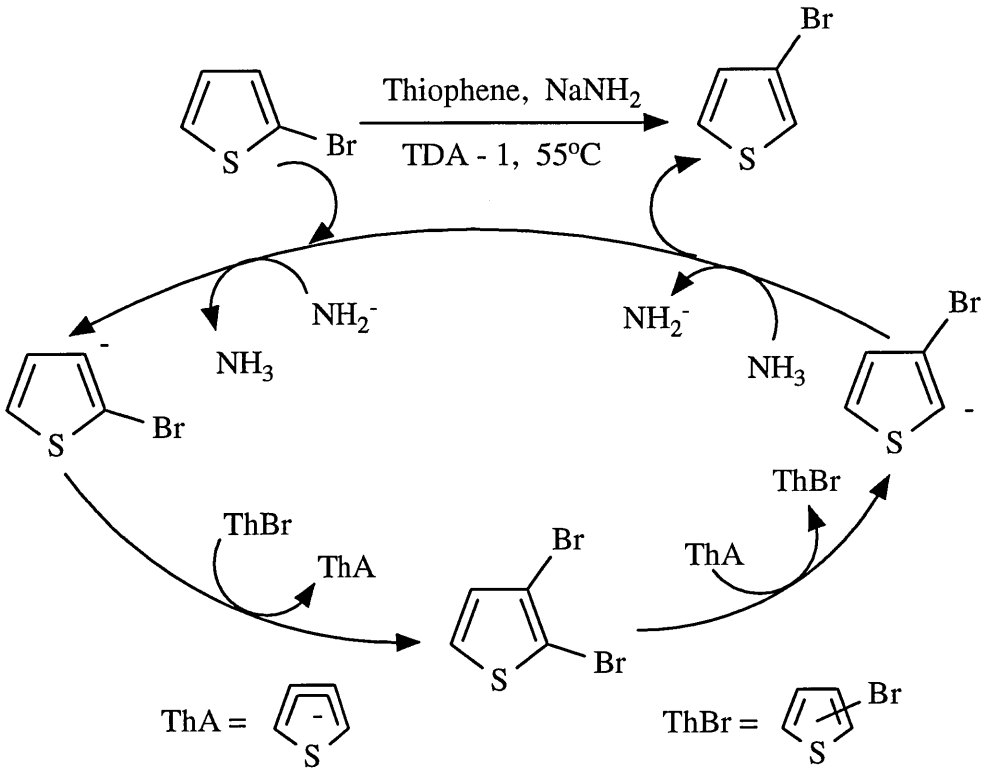


Graph 2.2 Production of 2BT vs Time



The graphs show that most of the 3BT is actually produced during the 1.5 hours at 55 °C. However, the reaction is continued in order to convert the remaining 2BT within the reaction mixture to 3BT. Also illustrated is how the reaction rate is substantially reduced at lower temperature, and also how, at lower temperature (25 °C and to a limited extent at 0 °C), ultrasound still provides a route to the product although significantly reduced in yield. The stirred equivalent of the reaction at this temperature is practically stopped.

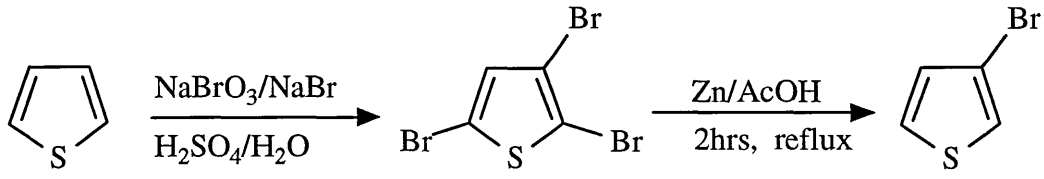
It is worthwhile to note that very little 25DBT is found in the reaction mixture even in the early stages of the reaction. The starting material is rapidly converted to 2BT by the sodamide, which is why it is not evident in the reaction mixture. The 2BT is in turn rearranged to 3BT by the sodamide. This is an example of an effect known as the "halogen dance"[348]. The mechanism is illustrated below [Scheme 132]. Initially sodamide removes a proton from the 3-position on the 2-bromothiophene to form the resultant anion and ammonia. This anion then reacts with another molecule of 2BT to give 2,3-dibromothiophene and the anion of thiophene. This anion can then remove the bromine atom at the 2-position to form the anion of 3-bromothiophene, which then obtains a proton from the ammonia produced earlier in the reaction to give 3-bromothiophene.



[Scheme 132]

2.4.2 Reduction of Tribromothiophene to 3BT.

An alternative route to 3BT mentioned above (Section 2.4.1) was the tribromination of thiophene using bromide/bromate and sulphuric acid, and the subsequent reduction of 2,3,5-tribromothiophene (235TBT) by refluxing with Zn/aqueous acetic acid for 2 hours to form 3-bromothiophene [Scheme 133].



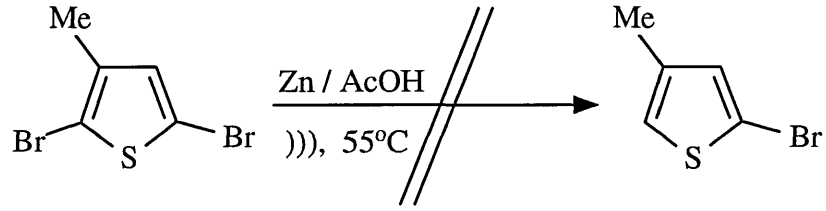
[Scheme 133]

It was the latter reaction that was considered for the application of ultrasound, since other heterogeneous reactions involving metals such as the Barbier and Grignard reactions[2] have been shown to benefit in terms of overall yield and conditions (mainly temperature and time).

To begin with, the standard reaction was repeated, which involved refluxing the 235TBT in zinc and acetic acid for 2 hours, steam distilling the organics out of the reaction and analysing the resultant product mixture by GC. This gave a good yield of 3BT with a very good 3BT:2BT selectivity of 99:1. Side products obtained were 2,4-dibromothiophene (24DBT) (2.5%), and 3,4-dibromothiophene (3%). This reaction was then repeated with sonication with the sonic probe at power setting 5. After working the reaction up the yield and selectivity were slightly less than the standard refluxed reaction (85%, 95:5). When this reaction was run it was found that little noise was produced by the probe. This can be easily explained when the action of cavitation is considered. If the reaction is refluxing it means that the internal vapour pressure has matched the external pressure, therefore the reaction mixture will be saturated with vapour. This vapour will fill any void that may be formed from the effect of ultrasound and hence cavitation will not occur to any great extent. This also illustrates that the audible noise created from the ultrasonic probe originates from the cavitation occurring within the solution, and not from the probe itself.

Considering that ultrasound had little effect on the refluxing reaction, the reaction was repeated at lower temperatures (75 °C, 50 °C, 25 °C) with both ultrasound and stirring only. As expected at the lower temperatures the reaction rate decreased and the yield was reduced. At 75 °C the stirred reaction gave a low yield of 3BT (25%), 24DBT

(5%), 3,4-dibromothiophene (34DBT) (3%), and 2,3-dibromothiophene (23DBT) (0.7%). The yield of 3BT was improved (40%) when the reaction was sonicated and similar side products were produced, 24DBT (4%), and 34DBT (2.5%). At 50 °C the stirred reaction gave 3BT (11%), 24DBT (5%), 34DBT (2%), 23DBT (1%), and the sonicated reaction gave 3BT (17%), 24DBT (11%), 34DBT (3%), and 23DBT (0.7%). The sonicated reaction produced a relatively greater amount of 24DBT, which was also found to a greater extent at the lower temperature of 30 °C. At 30 °C it was found the stirred reaction produced 3BT (6%), 24DBT (10%), 34DBT (1%), and 23DBT (2%). The sonicated reaction by comparison produced 3BT (5%), 24DBT (25%), 34DBT (7%), 23DBT (6%). Why 2,4-dibromothiophene should be produced at lower temperatures is not clear. This phenomenon was used in an attempt to produce 2-bromo-4-methylthiophene (2B4MT) which is difficult to make under normal conditions. The experiment above with ultrasound at 30 °C was repeated with 2,5-dibromo-3-methylthiophene as the starting material, in an attempt to produce 2B4MT. At the end of the experiment however no reaction had occurred according to GC.

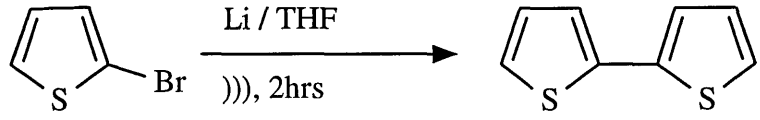


It was noticed that ultrasound with a suspension of zinc in water decolourised the starting material (crude raw product from tribromination of thiophene, i.e. crude tribromothiophene), which is believed to be a simple reduction of any impurities that may exist within the reaction mixture.

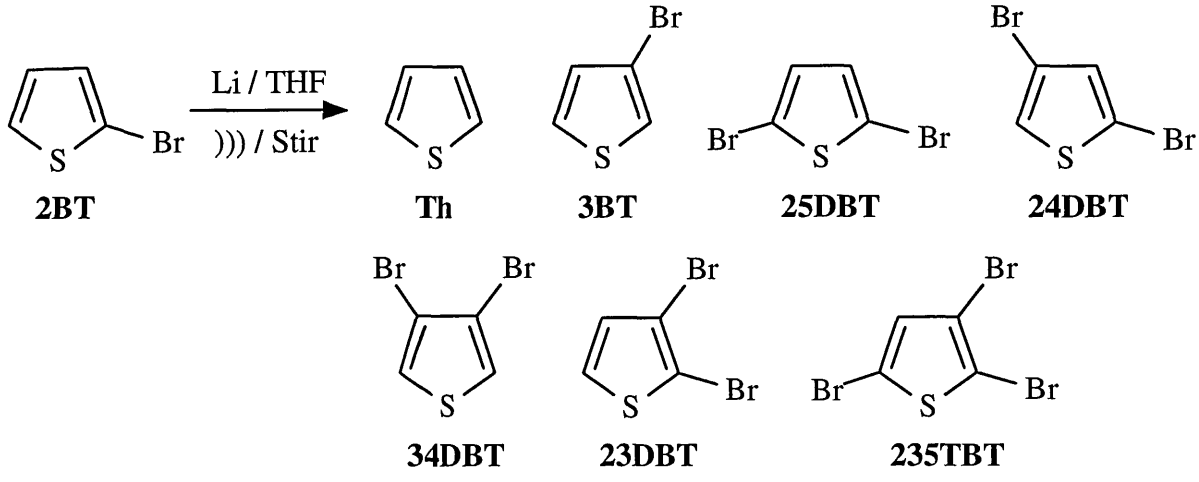
2.5.0 BROMOTHIOPHENE COUPLING

Introduction

Wurtz-type coupling of bromobenzenes[254] and bromopyridines[251] has been described in the literature. Considering the similarity of bromothiophene to these compounds it was considered logical to extend the scope of the reactions and attempt a similar synthesis with bromothiophenes. Initially, 2-bromothiophene was used as the starting material and later a limited investigation into other halothiophenes was pursued. The aim was to produce a dimer from 2-bromothiophene in a Wurtz-type coupling reaction.



Unfortunately, under all the reaction conditions attempted no products resulting from coupling were obtained. However, several products from halogen rearrangement of the starting material were obtained [Scheme 134]. Reactions similar to this are well known to occur with bromothiophenes under basic conditions[348-350].



[Scheme 134]

The reaction conditions that were examined in an effort to obtain bithiophene are discussed below.

Lithium metal

Initially 2-bromothiophene was sonicated (power setting 8) in dry THF at 35 °C for 2 hours with small pieces (approx. 5mm^3) of lithium that had been cut from a solid

piece of the metal. At the end of the reaction only starting material was present. This was not surprising because the pieces of lithium had adhered to the sonic probe and "climbed" up the probe effectively removing them from the reaction mixture. Why the lithium did this is unknown, but the lithium lumps were replaced with a granular form which stayed in the solution. When the reaction was carried out with the granular form of lithium a halogen rearrangement occurred to produce thiophene (41%), 3BT (3%), 23DBT (3.5%), and 24DBT (2.5%) along with 2BT (51%) which is unreacted starting material. When the same reaction was carried in the sonic cup horn a different bromothiophene ratio was obtained, thiophene (25%), 2BT (7%), 3BT (20%), 25DBT (0.5%), 24DBT (7%), 23DBT (5.5%), 34DBT (15%), tribromothiophene (TBT) (32%). This difference in product ratios could be explained by the round bottomed flask in the sonic cup horn having less temperature control than the flange flask which is used in the sonic probe reactions. Additionally, the ultrasonic densities in the two flasks will have a marked difference. When powdered lithium was used the product ratio changed again- thiophene (8%), 2BT (45%), 3BT (25%), 25DBT (1%), 24DBT (1%), 23DBT (1%), 34DBT (17%), TBT (1%). When the reaction was repeated with powdered lithium under quiet conditions it was mainly debromination to thiophene that occurred, with the product mixture shown to contain thiophene (20%), 2BT (70%), 3BT (3.5%), 25DBT (2%), 24DBT (3%).

Temperature

As in previous sections, the effect of temperature differences was studied during the reaction. When the reaction mixture was sonicated at 5 °C more starting material was debrominated and converted into the other bromothiophenes [thiophene (34%), 2BT (13%), 3BT (14%), 25DBT (3.5%), 24DBT (21%), 23DBT (9%), 34DBT (2%), TBT (3.5%)]. A similar result was obtained when the reaction was carried out at -50 °C by cooling the reaction mixture with an acetone/liquid nitrogen slush [thiophene (47%), 2BT (7.5%), 3BT (15%), 24DBT (10%), 23DBT (7.5%), 34DBT (7.5%), TBT (5%)]. Why the 5 °C and -50 °C sonicated reactions give similar product mixtures is unknown, the sonicated energy may reach a maximum in THF at a temperature of 5 °C or higher. When these reactions were repeated with stirring only, the main reaction that occurred was the debromination of the starting material into thiophene. At 5 °C the following product ratio was obtained for the stirred reaction, thiophene (39%), 2BT (60%), 3BT (1%), and at -50 °C thiophene (39%), 2BT (59%), 3BT (1%). When the reaction was refluxed with stirring only, the principal reactions were debromination to thiophene (28%), and rearrangement of 2BT (39%) to 3BT (19%), other products formed were 25DBT (2%), 24DBT (2%), 23DBT (1%), 34DBT (9%).

Iodothiophene Quench

It was hypothesised that the large amount of thiophene present in the final product ratios were in fact derived from lithiated thiophene which may have been formed from the reaction of bromothiophene with the lithium metal. If this was formed it would react with the methanol quench used in the work up to form thiophene and lithium methoxide. Therefore the stirred reaction at 35 °C was repeated but it was quenched initially with iodothiophene which would react with any lithiated thiophene that may exist to form the dimer bithiophene. However the product ratio was not changed with the iodothiophene quench, thiophene (21%), 2BT (70%), 3BT (2%), 25DBT (1.5%), 24DBT (0.5%), except for the formation of a small amount (5%) of bromo-iodothiophene.

n-Butyl Chloride

Another attempt was made to synthesise lithiated thiophene, which could then be quenched with bromothiophene to produce bithiophene. In this experiment thiophene, n-butyl chloride and lithium[240] were sonicated in the sonic cup horn for 2 hours, then quenched with bromothiophene. However no products other than starting materials were present.

Anthracene

Anthracene is known as an electron transfer agent[203,216] and it was employed to ascertain if it would have any effect on this reaction. When anthracene was added to the sonicated reaction at 35 °C it had a modest effect on the debromination and rearrangement reactions that had previously occurred [thiophene (26%), 2BT (7%), 3BT (42%), 25DBT (9%), 24DBT (6%), 23DBT (6%), 34DBT (3%)]. When anthracene was added to the stirred reaction at 35 °C it had little effect except preventing debromination to thiophene, the product ratios were 2BT (88%), 3BT (3%), 25DBT (3.5%), 24DBT (0.5%), 23DBT (0.5%), 34DBT (3%), TBT (0.5%). This limited experiment seemed to show that when anthracene was added to the sonicated reaction 3BT production was enhanced, which tentatively suggests that a radical mechanism is involved. To extend this hypothesis radical quenchers were examined. However it was considered they would react with the lithium, e.g. phenol, p-cresol, O_2, which limited their use. This phenomenon was interesting and deserved further investigation, however since radical/anion mechanisms were not the aim of this project, this area was not investigated further.

Thiophene

In the rearrangement of 2,5-dibromothiophene to 3-bromothiophene discussed earlier, thiophene was used as a solvent and as a halogen transfer agent. Therefore thiophene was examined as a solvent instead of THF and also as a co-solvent with THF in an attempt to alter the reaction products. Thiophene was therefore used as a solvent when the reaction was sonicated (power setting 9 & 10) and also when the reaction was refluxed (2 hours), but these reaction conditions produced only starting material at the end of the reaction. A thiophene/THF solvent system was also used in the reaction. This solvent mixture was used with the reagents while sonicated (power setting 10) at 35 ^{0}C and at 50 ^{0}C for 2 hours, but only starting material was present at the end of the reaction. The only reaction that occurred with this solvent system was when it was refluxed. After 2 hours some of the starting material, 2BT (58%), had debrominated to thiophene (40%), and the remainder rearranged to 3BT (1.5%). These results prompt the suggestion that THF plays a part in the "halogen dance" that occurs in the previous reactions, which is absent when thiophene is used as the solvent.

Ullman Coupling

Lindley *et al*[221] have reported the Ullmann coupling of aryl halides using an excess of copper in DMF. No success was obtained using 2-bromothiophene and 2-chlorothiophene as the starting materials and sonicating them with an excess of copper flitters.

Sodium

When lithium was replaced with sodium wire in the reaction and sonication was applied (power setting 5) at 25 ^{o}C for 30 minutes, similar reactions occurred although the product ratio was different [thiophene (47%), 2BT (16%), 3BT (10%), 25DBT (1%), 24DBT (5.5%), 23DBT (4.5%), 34DBT (5%), TBT (10%)]. When the same reaction was refluxed for 2 hours without ultrasound the principal reaction was the debromination to thiophene (20%), the other products formed were 3BT (5%), 25DBT (1%), 24DBT (1%), 34DBT (1.5%) along with recovered starting material (70%). When the reaction mixture was stirred at room temperature without ultrasound no reaction occurred. Therefore in this case ultrasound does have an effect, albeit random bromo rearrangements.

3-Bromothiophene

Sonicating 3-bromothiophene with lithium in THF debrominated 3-BT to thiophene (17%) with some rearrangement to 2-BT (1%), along with recovered starting material (82%). This was also found when the reaction mixture was refluxed, thiophene (6%), 3BT (94%). Sonicating 3-BT with sodium produced a similar result, thiophene (26%), 2BT (1%), 3BT (73%).

2,5-Dibromothiophene

2,5-Dibromothiophene was sonicated with lithium in THF in the sonic cup horn at 25 °C for 2 hours. This produced a complex mixture of halothiophenes with the main products being 34DBT (16%), 2BT (28%), TBT (23%), and starting material (26%). The reflux equivalent indicates a similar product distribution but a slower reaction rate, 25DBT (65%), 34DBT (4%), 2BT (20%), thiophene (6%), TBT (5%).

2-Chlorothiophene

A final reaction of this type was the sonication (power setting 5) of 2-chlorothiophene with lithium granules at 30 °C using the sonic cup horn. This only succeeded in dechlorinating 10% of the starting material into thiophene.

2.6.0 2-METHOXYTHIOPHENE PREPARATION - 2BT METHOXYLATION.

The preparation of 2-methoxythiophene (2-MeOTh) in the literature[351,352] uses 2BT as the starting material and the product is obtained by nucleophilic displacement with methoxide utilising copper salts as catalysts. Unfortunately these procedures involved long reaction times (30hrs) and incomplete conversion of 2BT. SCL has developed a synthetic route[353] for the commercial production of 2-methoxythiophene by the reaction of 2-bromothiophene with sodium methoxide/methanol solution in the presence of a complex mixed catalyst system, CuO/copper acetyl acetonate/TDA-1/KI. This reaction gives virtually 100% conversion of 2BT to the methoxy derivative with up to 80% molar yields and no major by-products.

In an effort to find a simpler reaction catalyst for this reaction, different catalysts were tried with ultrasound and compared to the equivalent refluxed reaction. The reaction conditions and products obtained are summarised below [Table 2.12].

Table 2.12 2BT Methoxylation

	Conditions	**Products**
		(remainder SM).
a)	Cu wire, MeONa,))) PS6, 55°C, 2hrs	Trace MeOTh.
b)	Cu wire, MeONa,))) PS8, 30°C, 2hrs	Trace MeOTh.
c)	Cu wire, MeONa, reflux, 25hrs	10% Th, 4% MeOTh.
d)	As **b)**,except Cu flitters	2% MeOTh.
e)	As **d)** with KI, PS5	9.5% MeOTh
f)	As **d)**, using DMF as solvent	Trace MeOTh, 30% 25DBT.
g)	CuO, MeONa,)))PS8, 30°C, 2hrs	3% MeOTh
h)	As **e)** with KI	24% MeOTh
i)	Repeat of **h)**	17.5% MeOTh
j)	Repeat of **h)** @ 50°C	7.5% MeOTh
k)	As **h)**,))) PS5, 15°C	3% MeOTh
l)	As **h)** - except in sonic cup horn	SM only
m)	As **h)** - stirred only	6% MeOTh
n)	NaOMe, KI, $Cu(acac)_2$,CuO, TDA-1 MeOH, (SCL METHOD) refluxed 14 hrs.	40% MeOTh
o)	As **n)** -))) PS8, 2hrs, 30°C	11.2% MeOTh
Phenoxylation.		
p)	DMF, Cu flitters/phenol, sonic cup sonic cup horn, 8hrs.	SM only

Initially, (Table 2.12, reaction a) 2BT was sonicated (power setting 6) with the sodium methoxide/ methanol solution at 55 °C for 2 hours to produce only a trace of 2-methoxythiophene (2MeOTh). This yield was not improved upon when the reaction temperature was decreased to 30 °C and the ultrasonic intensity increased to power setting 8 (Table 2.12, reaction b). When this reaction was refluxed with no ultrasound for 25 hours a small amount (4%) of 2MeOTh was produced along with thiophene (10%) (Table 2.12, reaction c).

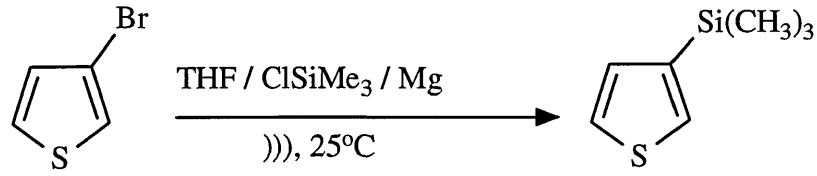
When the copper wire was replaced with copper flitters (Table 2.12, reaction d), and the reaction mixture was sonicated (power setting 8) for 2 hours at 30 °C, this produced a small amount of 2MeOTh (2%). When potassium iodide (Table 2.12, reaction e) was added to the reaction with copper flitters the yield of 2MeOTh improved but was still low (9.5%). DMF was used as an alternative to THF in an attempt to create a higher cavitation intensity. When 2BT was sonicated (power setting 8) with copper flitters in DMF (Table 2.12, reaction f) for 2 hours no 2MeOTh was produced, but a relatively high percentage of 25DBT was obtained. When the copper flitters and KI were replaced with CuO (Table 2.12, reaction g) a low yield (3%) was produced when the reaction was sonicated (power setting 8). However when KI was added to this reaction the yield increased 6 to 8 fold (24% and 17.5%) (Table 2.12, reactions h and i). When the temperature of the reaction was increased to 50 °C (Table 2.12, reaction j) the yield decreased (7.5%) under sonication conditions (power setting 8). Also, when the power setting was decreased (power setting 5), (Table 2.12, reaction k) the yield decreased (3%). Using the sonic cup horn (Table 2.12, reaction l) as the ultrasound source produced no MeOTh. When the reaction was stirred at room temperature (Table 2.12, reaction m) for 2 hours a small amount of 2-MeOTh (6%) was produced, which suggests that the sonic cup horn experiment was below any ultrasonic threshold that existed, and also that the ultrasound that was present was not agitating the solution enough for any efficient stirring to occur. The reagents normally used at SCL to produce 2-MeOTh, involves refluxing a reaction mixture consisting of 2BT, methanolic sodium methoxide solution, potassium iodide, copper acetyl acetonate, copper oxide, and phase transfer catalyst (TDA-1) for 18 hours. When this reaction mixture was refluxed for 14 hours (Table 2.12, reaction n) a moderate yield (40%) compared to the plant scale reaction was achieved. This is assumed to be due to differences in addition times of the various catalysts, which are optimised on the production method. However when this same reaction mixture was simply sonicated at 30 °C for 2 hrs (Table 2.12, reaction o) as a comparison to the refluxed reaction a poor yield (11.2%) of product was obtained. Therefore in this simple experiment the best catalyst system for the sonicated reactions was copper oxide with potassium iodide, which produced an average yield of 21% (24%, and 17.5% when repeated).

In an attempted Ullmann-type[221] phenoxylation reaction, 2BT was sonicated in the sonic cup horn for 8 hours with phenol and copper flitters in DMF for 8 hrs (Table 2.12, reaction p). At the end of this period no reaction had occurred.

2.7.0 SILYLATION OF BROMOTHIOPHENES

2.7.1 3-BROMOTHIOPHENE

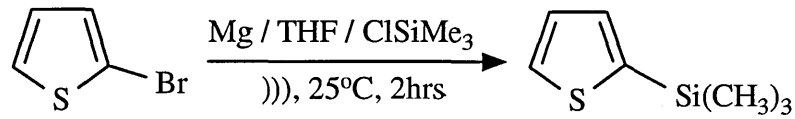
Goldberg *et al*[354] have reported the synthesis of 3-thienyltrimethylsilane using ultrasound. 3-Bromothiophene was sonicated with trimethylsilyl chloride and magnesium suspended in THF to form the product in good yield (75%) within 8 hrs. This compares to previous methods which took up to 43 hrs[355] or used more powerful reducing agents such as sodium sand[356].



This reaction was repeated using a 38kHz Kerry ultrasonic cleaning bath for 8 hrs, a sonic cup horn (20kHz) for 5 hrs, and a sonic probe (20kHz) for 2 hrs. None of these methods produced any silylated product and all that was observed was starting material. This may be a frequency effect since Goldberg used 45kHz, but this is comparable to the Kerry ultrasonic bath frequency, therefore the ultrasonic equipment used may have a higher power capability. It has been reported that metal purity can have an effect on reaction between trimethylchlorosilane and lithium e.g. using 2% Na in lithium rather than the pure metal[357]. However, it was found that the sodium content affected only the stirred reaction, which did not proceed with pure lithium metal. The sodium was believed to react rapidly and kept the surface of the lithium exposed which, in turn, enhanced the reaction rate. The sonicated reaction gave good yields whether sodium was present or not, thus illustrating the surface cleaning properties of ultrasound once more. Therefore metal purity does not explain the experimental difference observed in the attempted synthesis of 3-thienyltrimethylsilane.

2.7.2 2-BROMOTHIOPHENE

It was found that when 2-bromothiophene was sonicated in the sonic cup horn (power setting 2), 2-trimethylsilylthiophene (100% GC, 73% isolated yield) **(173)** was readily formed within 15 mins [Table 2.13, reaction a].



(173)

Table 2.13 Silylation of 2-Bromothiophene

	Products (% yield)			
Conditions	2BT	2-$(CH_3)_3$SiTh	Thiophene	Bithiophene
a)))), rt, 15min,		100		trace
b) Stir, rt, 7hrs	26	74		
c) Stir, rt, 32hrs, 1.25 eq. TMSCl		96		4
d) Stir, reflux, 2hrs	16	66	18	
e) Stir, reflux, 5hrs, 1.5 eq. TMSCl, 1.5 eq. Mg	5	48	47	

eq. = equivalents

The reaction was repeated with stirring only at room temperature (Table 2.13, reaction b), which gave 2-trimethylsilylthiophene (74%) **(173)**, after 7 hrs, with the remainder consisting of starting material. To examine how long the stirred reaction would take to go to completion at room temperature it was repeated with sampling and additional TMSCl (0.25 equiv. extra) (this was to ensure it was not depleted since it is very volatile). After 24 hrs, 2BT (5%) remained, after 32 hrs the reaction had gone to completion (96%, gc) and a small amount of bithiophene (4%) was present (Table 2.13, reaction c). The production of bithiophene may be a reaction between the silylthiophene and 2-bromothiophene to form the dimer *via* a Grignard type intermediate. The initial reaction was repeated under reflux conditions over 2hrs and gave a mixture of thiophene (18%), 2BT (16%), and 2-(trimethylsilyl)thiophene (66%) **(173)** (Table 2.13, reaction d). Hexamethylsiloxane was detected in the reaction mixture (which is produced from the aqueous quench when TMSCl is present), indicating that the reaction had not gone to completion. The reaction was repeated over a longer time period with sampling throughout to monitor the progress

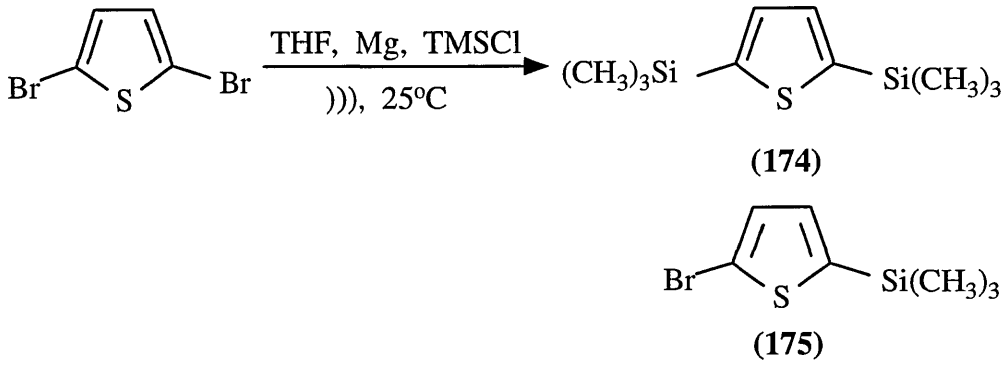
of the reaction (Table 2.13, reaction e). Little change in the product ratio was observed when the reaction was continued through 2.5 hrs and 3.5 hrs so extra trimethylsilyl chloride (0.5 equiv.) was added in an effort to force the reaction forward, however the reaction mixture was not changed after 4 hours. At this point extra magnesium was added which only succeeded in reducing 2BT and 2-(trimethylsilyl)thiophene **(173)** into thiophene. After 5 hrs the product mixture was thiophene (47%), 2-bromothiophene (5%) and 2-(trimethylsilyl)thiophene (48%) **(173)**.

Conclusions

When compared with stirring, ultrasound produces 2-(trimethylsilyl)thiophene **(173)** in good yield (73% isolated) within 15 mins at room temperature, whereas the stirred equivalent takes 32 hrs to complete. Refluxing the stirred reaction increases the reaction rate but also promotes reduction to thiophene.

2.7.3 2,5-DIBROMOTHIOPHENE

2,5-Dibromothiophene (25DBT) was subjected to the same conditions as 2-BT in an attempt to produce the disilylated product **(174)**.



[Scheme 135]

25DBT was sonicated in the sonic cup horn (power setting 2) with magnesium and TMSCl in THF, using one equivalent of both reagents (one equivalent per bromine) (Table 2.14, reaction a). After 2hrs sonication bis-2,5-(trimethylsilyl)thiophene (58%) **(174)** and 2-(trimethylsilyl)thiophene (17%) **(173)** were produced along with the minor components 2-bromo-5-(trimethylsilyl)thiophene (2%) **(175)** and 2-bromothiophene (4%). It was not possible to identify the remaining components of the reaction mixture, based on the available mass spectral data.

Excess Reagents

Additional magnesium and TMSCl (2 equivalents each) were added to the reaction (Table 2.14, reaction b). The effect on the reaction was to reduce the minor components and boost the concentration of the silylated products 2-(trimethylsilyl)thiophene (33%) **(173)** and bis-2,5-(trimethylsilyl)thiophene (67%) **(174)**. A similar product distribution was obtained when additional magnesium (2 equivalents) only was added to the reaction (Table 2.14, reaction c) with the only two products again being 2-(trimethylsilyl)thiophene (28%) **(173)** and bis-2,5-(trimethylsilyl)thiophene (72%) **(174)**. When 2 equivalents of TMSCl were added with only 1 equivalent of magnesium (Table 2.14, reaction d) the reaction did not go to completion with a significant amount of starting material left (18%), along with the other products 2-(trimethylsilyl)thiophene (13%) **(173)**, bis-2,5-(trimethylsilyl)thiophene (64%) **(174)**, and 2-bromo-5-(trimethylsilyl)thiophene (5%) **(175)**. However, this could have been due to the reduced reaction time not allowing the reaction to go to completion.

Reflux

The reaction was repeated under reflux (Table 2.14, reaction e), with sampling and analysis by GC-MS to monitor the reaction. After 2 hrs, thiophene (29%), 2-(trimethylsilyl)thiophene (15%) **(173)**, 2,5-dibromothiophene (12%) and bis-2,5-(trimethylsilyl)thiophene (44%) **(174)** were present. The reaction was continued for a further 3 hours and this had the effect of reducing more bromo compounds to thiophene (38%), the remainder of the reaction mixture was 2-(trimethylsilyl)thiophene (17%) **(173)**, 2,5-dibromothiophene (11%) and bis-2,5-(trimethylsilyl)thiophene (51%) **(174)**.

Solvent Variables

The volume of THF was halved to increase the rate of reaction (Table 2.14, reaction f), and after 15 mins the reaction started to turn into an immobile sludge which became brown in colour and the reaction had to be stopped. This increased the amount of bis-2,5-(trimethylsilyl)thiophene (75%) **(174)**, but other side products were produced, 2-(trimethylsilyl)thiophene (11%) **(173)**, 2-bromo-5-(trimethylsilyl)thiophene (6%) **(175)**, 2-bromothiophene (1%) and starting material (7%). The conditions with excess reagents (2 equivalents) was repeated with reduced THF (50%) (Table 2.14, reaction g) but gave a similar product ratio to that seen in the reduced THF experiment (f), and this reaction also had to be stopped after 15 minutes for the same reasons. Therefore, in both these cases where the amount of

solvent is decreased, effectively increasing concentration, the reaction rate is improved and the product distribution improved, but the reaction mixture begins to decompose.

In an attempt to reduce decomposition the original reaction was repeated with additional THF (1.5 times original amount) (Table 2.14, reaction h) to give a good yield of bis-2,5-(trimethylsilyl)thiophene (83%) **(174)**, with a smaller amount of 2-(trimethylsilyl)thiophene (17%) **(173)**. The reaction mixture was diluted even further (2.5 THF) (Table 2.14, reaction i) and although this reduced the production of the bis-2,5-(trimethylsilyl)thiophene (23%) **(174)** and 2-(trimethylsilyl)thiophene (9%) **(173)**, these conditions dramatically increased the production of 2-bromo-5-(trimethylsilyl)thiophene (61%) **(175)**, with the remainder of the reaction mixture containing 2-bromothiophene (5%) and starting material (2%). Although the reaction rate is reduced, 2-bromo-5-(trimethylsilyl)thiophene (35%) **(175)** is produced in an even greater ratio compared to the other reaction products bis-2,5-(trimethylsilyl)thiophene (2.5%) **(174)**, 2-(trimethylsilyl)thiophene (1.5%) **(173)**, 2-bromothiophene (6%) and the remainder being starting material (55%), when the concentration of reactants is reduced by half (effectively doubling solvent amount) (Table 2.14, reaction j). When these reaction conditions are repeated over 7 hours (Table 2.14, reaction k) the major component of the reaction mixture is the 2-bromo-5-(trimethylsilyl)thiophene (77%) **(175)**, with the remainder being starting material (9%), and 2BT (13%).

There is an obvious concentration effect where the 2-bromo-5-(trimethylsilyl)thiophene **(175)** is produced at lower concentrations of reagents. At the higher concentrations of reagents this product is not observed since the bromine atom will react with the reagents to produce the bis-2,5-(trimethylsilyl)thiophene **(174)** compound or the reduced monosilyated compound **(173)**.

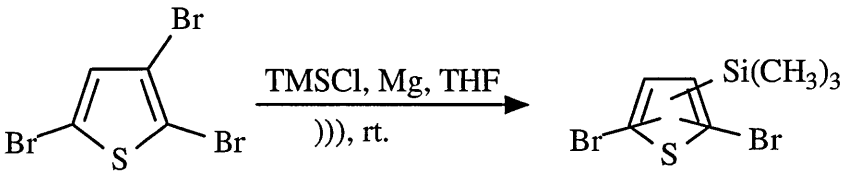
Table 2.14 Silylation of 2,5-Dibromothiophene

	Conditions	Th	SiTh	DBTh	DSiTh	BrSiTh	2BT
a)	))), 2hrs, r.t		17		58	2	4
b)	))), 2hrs, 2 eq		33		67		
c)	))), 1hr, 2 eq Mg only		28		72		
d)	))), 20min, 2 eq TMSCl only		13	18	64	5	
e)	Reflux, 5hrs	38	17	11	34		
f)	))), 15min, 1eq, 0.5 THF		11	7	75	6	1
g)	))), 15min, 2eq, 0.5 THF		18	7	70	4	
h)	))), 20min, 2eq, 1.5 THF		17		83		
i)	))), 90min, 2eq, 2.5 THF		9	2	23	61	5
j)	))), 2hrs, 4eq, 5 THF		1.5	55	2.5	35	6
k)	))), 7hrs, 4eq, 5 THF			9		77	13

Th = Thiophene, SiTh = 2-(trimethylsilyl)thiophene, DBTh = 2,5-dibromothiophene
DSiTh = bis-2,5-(trimethylsilyl)thiophene, BrSiTh = 2-bromo-5-(trimethylsilyl)thiophene
eq = Number of equivalents of reagent per bromine atom

2.7.4 2,3,5-TRIBROMOTHIOPHENE

As with the bromothiophenes above, tribromothiophene was sonicated in the sonic cup horn for 2hrs with magnesium and TMSCl in THF. After 2hrs GC-MS indicated a crude product mixture consisting of 2,5-dibromothiophene (6%), two bromo(trimethylsilyl)thiophenes (3%, 2%), tribromothiophene (8%), two dibromo(trimethylsilyl)thiophenes (24%, 53%) (**176**), and an unknown fraction (m/z 364, 4%) (these compounds were not isolated, hence the ring positions of substituents are not specified).



(176)

Table 2.15 Silylation of 2,3,5-tribromothiophene

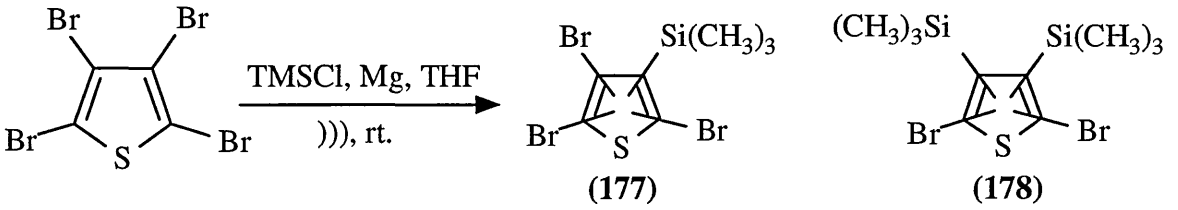
	Conditions	DBTh	BrSiTh	TBT	DBrSiTh	3BT
a)	))), 4hr	6	2, 3	8	25, 55	
b)	))), 2hr, 0.5 THF	1.5	5.5, 3.5		13, 77	2
c)	Reflux, 2hr, 0.5 THF	10	7, 7		27, 45	

BrSiTh = bromo(trimethylsilyl)thiophene, DBTh = dibromothiophene
DBrSiTh = dibromo-(trimethylsilyl)thiophene

Sonicating the reaction mixture for a further 2hrs had little effect except to remove the unknown compound, m/z 364 (Table 2.15, reaction a). The concentration of the reactants was doubled and the conditions above repeated for 2hrs (Table 2.15, reaction b). This had the effect of increasing the total amount of the two dibromo(trimethylsilyl)thiophenes (13%, 77%) **(176)**, the remainder of the reaction mixture was made up of dibromothiophene (1.5%), and the two bromo(trimethylsilyl)thiophenes (5.5.%, 3.5%). When this reaction was refluxed for 2hrs with stirring (Table 2.15, reaction c), less dibromo(trimethylsilyl)thiophenes **(176)** were produced (27%, 45%) and selectivity for the second of these two isomers was reduced. Other products in the reaction mixture were identified from their retention times and molecular ion on gc-ms as two bromo(trimethylsilyl)thiophenes (7%, 7%), 2,5-dibromothiophene (10%), and 3-bromothiophene (2%). Overall tribromothiophene can only be silylated at one of the bromine positions, which is surprising considering that 2,5-dibromothiophene can be silylated at both halogen positions. Which halogen is preferentially silylated is not known since the product mixture was not separated. This limited study illustrates the reduced selectivity that occurs when more than one position on the ring of the starting material can react with the reagent.

2.7.5 TETRABROMOTHIOPHENE

Tetrabromothiophene was sonicated using a sonic cup horn (power setting 2) at room temperature for 2 hours with magnesium and trimethylchlorosilane in dry THF [Scheme 135]. GC-MS indicated the major product was tribromo-(trimethylsilyl)thiophene (59%) **(177)**, followed by dibromo-bis-(trimethylsilyl)thiophene (25%) **(178)**, dibromo-(trimethylsilyl)thiophene (12%) **(176)**, tribromothiophene (4%), and dibromothiophene (1%). These compounds were not isolated therefore the ring positions of the functional groups are unknown.

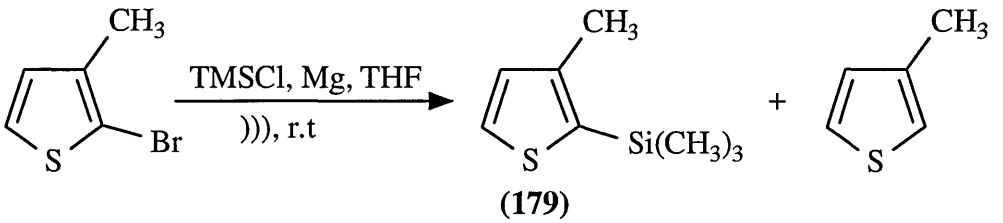


[Scheme 136]

The reflux equivalent of the above gave a similar product mixture, except for a reduction in the amount of the tribromo(trimethylsilyl)thiophene (42%) **(177)** and an increase the amount of dibromo(trimethylsilyl)thiophene (25%) **(176)**. The other components in the reaction mixture were dibromo-bis-(trimethylsilyl)thiophene (26%) **(178)**, tribromothiophene (5.5%), and 2,5-dibromothiophene (2.5%). This reaction again illustrates the selectivity problems that can occur when the reaction involves a starting material with several ring substituents.

2.7.6 2-BROMO-3-METHYLTHIOPHENE

2-Bromo-3-methylthiophene (2B3MT) was successfully silylated when it was sonicated in the sonic cup horn for one hour with TMSCl and magnesium in THF [Scheme 136]. This produced 3-methyl-2-(trimethylsilyl)thiophene **(179)** (3M2TMSTh) (59%, GC), along with the debrominated starting material 3-methylthiophene (3MT) (18%, GC), and other unidentified minor products (Table 2.16, reaction a). Due to their volatility, isolation of these compounds proved to be difficult, however, isolation did prove to be possible by bulb to bulb distillation.



[Scheme 137]

Table 2.16 Silyation of 2-Bromo-3-methylthiophene

	Conditions	MeTh	MeSiTh
a)	))), 1hr	18	59
b)	))), 1hr, 2eq Mg only		86
c)	))), 1hr, 1.5 eq Mg, 1.1 eq TMSCl	33	67
d)	Reflux, 2hrs, 1.5 eq Mg, 1.1 eq TMSCl	15	85

MeTh = 3-methylthiophene, MeSiTh = 3-Methyl-2-(trimethlsilyl)thiophene

The initial experiment was repeated with an excess of magnesium (2 equivalents) which improved the yield (86% not isolated) and produced an unknown component as the remainder (m/z 156) (Table 2.16, reaction b). Using excess magnesium (1.5 equiv) and TMSCl (1.1 equiv.) produced 3M2TMSTh (67%) and 3MT (33%) (Table 2.16, reaction c). After work up and isolation this afforded a moderate yield (57%) of the silylated product. However when this reaction was carried out using reflux (Table 2.16, reaction d) the yields of 3M2TMSTh (85%) and 3MT (15%) represented an improvement over sonicated reactions. The isolated yield of the silylated product 3-methyl-2-trimethylsilylthiophene improved to 76%.

This illustrates that ultrasound has no improved effect over reflux in this reaction which suggests that the reaction readily occurs thermodynamically.

2.8.0 CALORIMETRY

Introduction

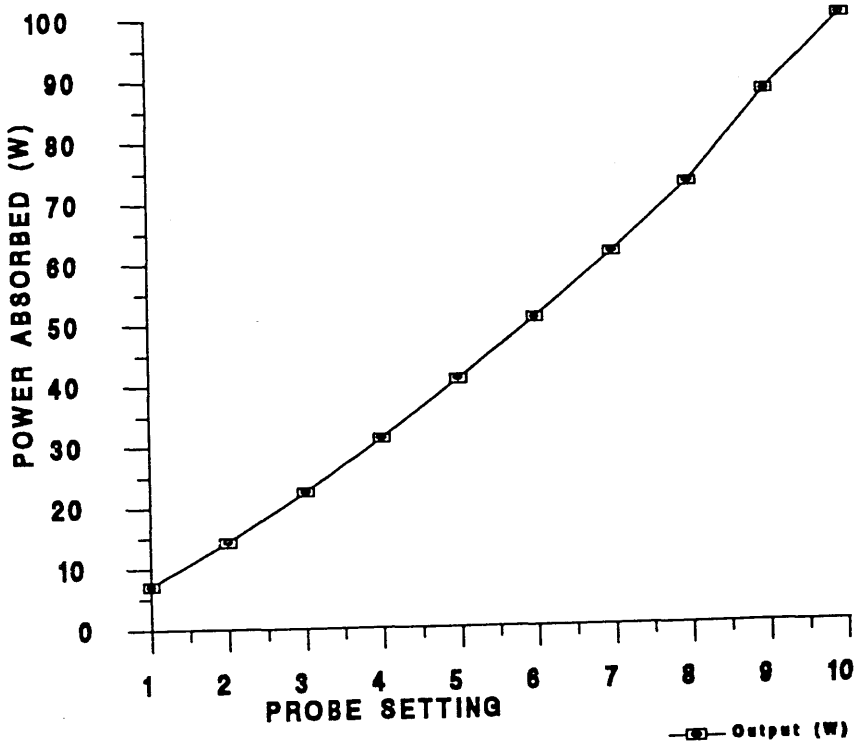
Although ultrasonic equipment is rated in terms of its output, usually in watts, this does not directly relate to the output into solution in terms of actual acoustic power. Often a machine rated at 600W will deliver only 100W actual acoustic energy into the system. There are several methods of measuring the acoustic output of ultrasonic equipment into a medium. There are physical means[358] such as calorimetry, measurement of vibrational amplitude, measurement of the real electrical power to the transducer, and particle size reduction[359]. There are also chemical methods which use dosimeters to measure the rate of radical production[360], or the dosimeters may be compounds whose decomposition[21,361] into other substances can be measured analytically to provide an accurate comparison of cavitation intensity. These different methods of measurement can be used to obtain consistency between one set of experimental conditions and another.

An excellent opportunity occurred at SCL to measure output from the probe. A Mettler RC1 calorimeter was made available for the calorimetric measurement of the output of the probe under various conditions. The output was measured for various probe depths, solvents, power settings, temperatures. Pulsed ultrasound, and detuning effects were also studied.

2.8.1 PROBE SETTING

It was not known at the outset if the ultrasonic probe gave a linear output over its full power range, and indeed, the actual output of the probe in real terms (compared to electrical rating) had not been ascertained. In order to determine both these parameters the ultrasonic probe was inserted into the jacketed flask of the calorimeter and water (1250ml) was charged to the vessel. The vessel was then calibrated at 20°C for ten minutes before the measurement on the probe was carried out. The initial run at power setting 1 was taken over 30 minutes, but this was considered excessive since the output did not vary over this time period. Therefore, the measurements were recorded over a time period of ten minutes from power setting 2 upwards. The resultant integral from the plot of output versus time is measured in joules and when this is divided by the time (s) gives the output of the probe in watts (Js^{-1}).

Graph 2.3 Power Setting

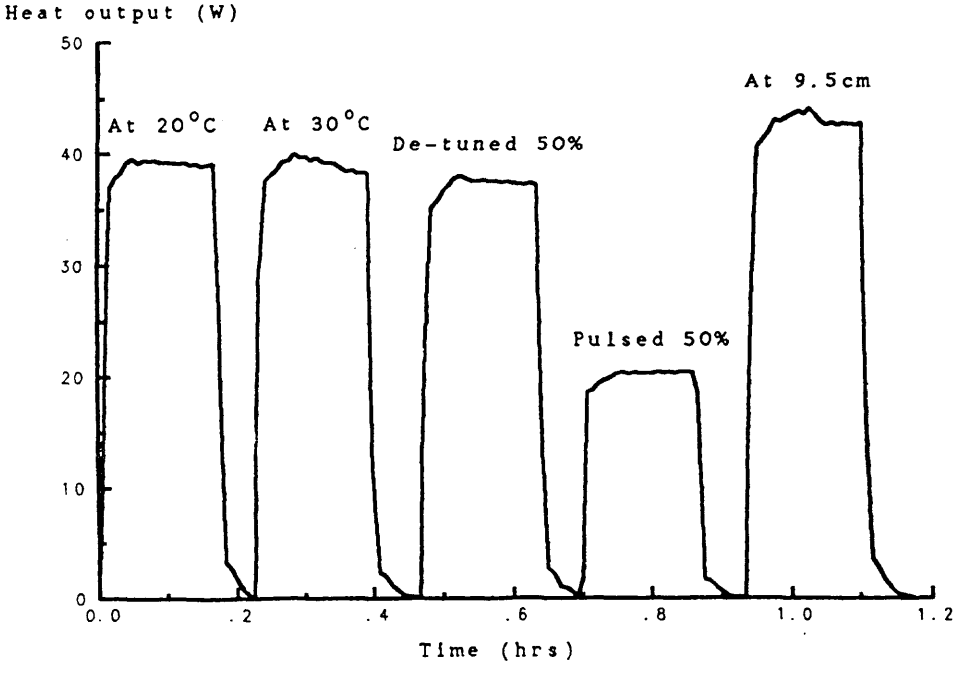


Once the output of the probe had been measured over its range, the output was measured at 30°C at power setting 5, when this measurement is compared to the one done at 20°C there is a decrease in energy output, which gives some indication that power output varies with temperature. The probe was then "detuned" by reducing by approximately 50% the output value on the meter of the amplifier. As would be expected this resulted in a decrease in the probe output. A recheck of the output at 20°C confirmed that the measurements were consistent. An extra amount of water (250ml) was added simply to observe the difference, if any, in the output from the probe, again the output did increase. This extra water had the effect of immersing more of the probe in the liquid, and the fact that the total power increased from the probe suggests that ultrasonic energy is being emitted from along the length of the probe as well as the tip. Graph 2.4 shows several traces from the calorimeter illustrating the power absorbed into the solution from the probe

This short study illustrated that the probe's output had a very slight upward curve with increased power setting (Graph 2.3), but it was practically indeed linear. It also showed that probe depth and temperature could have an effect on the amount of energy passed into the solvent (Graph 2.4).

It was noted that an initial effect of the ultrasound was to degas the solvent, this degassing also took place in the oil jacket around the vessel. This degassing did not have any effect on the power output throughout any of the measurements carried out.

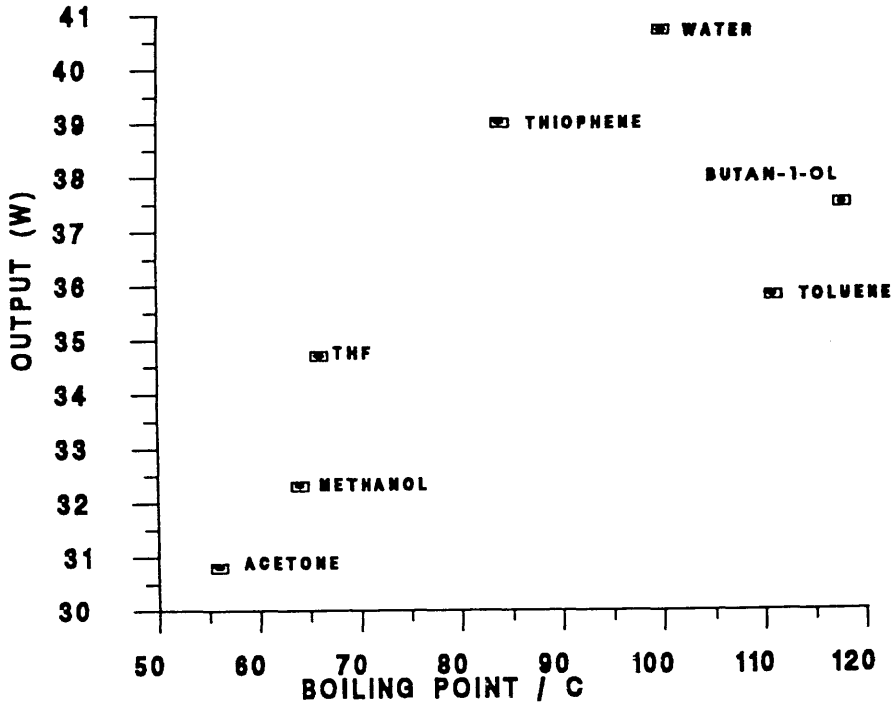
Graph 2.4 Various Parameters



2.8.2 SOLVENTS

From previous work[2,6] it is considered that the solvent of choice for an ultrasonic reaction can affect the ultrasonic intensity that is imparted into the system. Therefore various solvents (1250ml) were separately charged to the calorimeter vessel. After calibration at 20 °C, the probe was turned on for 10 mins. at power setting 5 at a depth of 7.1 cm (measured from the probe tip to where the surface of the solvent met the probe's side). The results of the heat output from the probe into solvents are shown in Graph 2.5 of heat output versus boiling point. This shows that, in general terms, power absorbed by the solvent increases with boiling point.

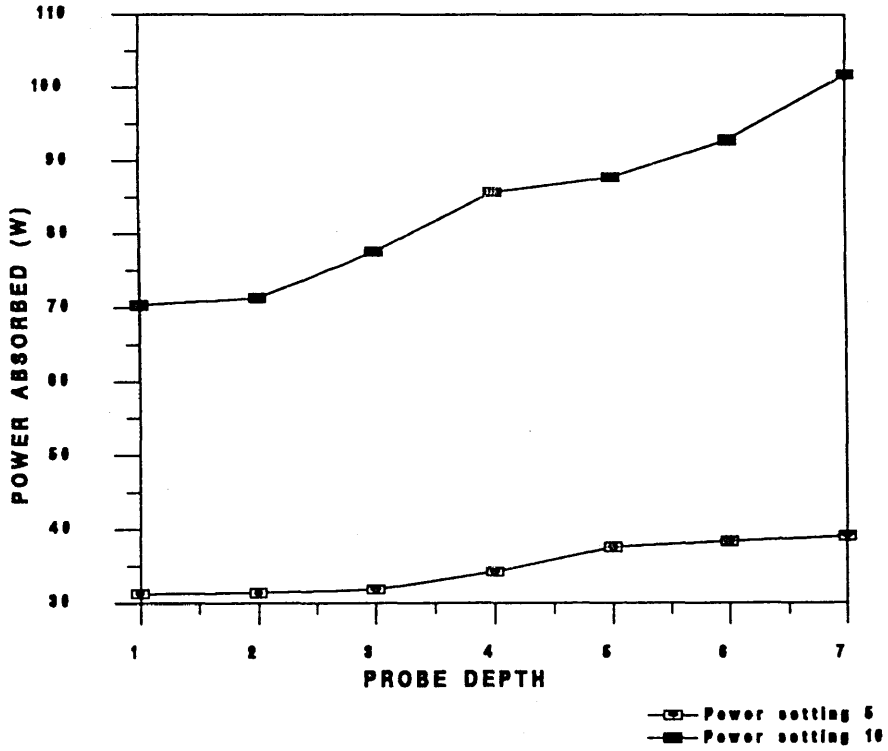
Graph 2.5 Solvents



2.8.3 PROBE DEPTHS

The initial study indicated that small amounts of acoustic energy could be emitted along the length of the sonic probe. Therefore the probe was immersed at different levels into water and its output measured. Water (1250ml) was charged to the vessel. After calibration at 20 °C, the probe was turned on for 10 mins. at power settings 5 & 10 at depths of 1cm to 7cm (distance from water level to tip) in steps of 1cm. It was found that for this sonic horn most of the power is emitted through the tip and is found to be 50-55W/cm^2 (based on a diameter of 12mm and surface area of 1.13cm^2). However it can be seen that a significant amount is also emitted along the length of the probe, which has a "blip" between 3 and 5 cm. These results could be due to a slight detuned effect. The probe (13.8cm) is not an exact multiple of the wavelength of sound in titanium (14cm) some of the ultrasonic energy could dissipate from the side of the probe.

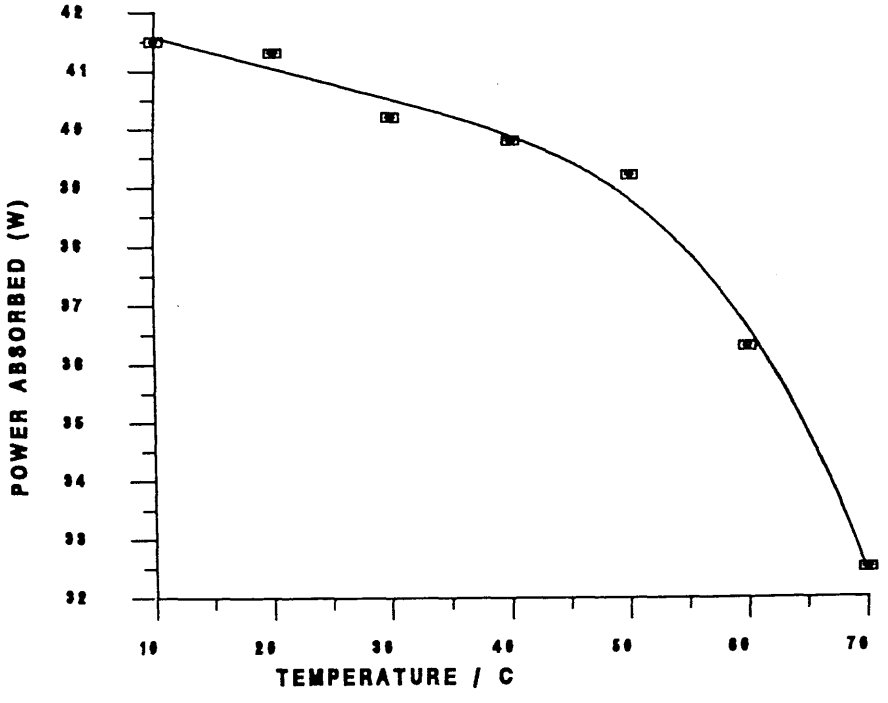
Graph 2.6 Probe Depths



2.8.4 TEMPERATURE

It is known that sonicated reactions often proceed faster at lower temperatures[2,6]. It is believed that at higher temperatures the increased vapour pressure of the liquid causes migration of vapour into the voids created by ultrasound, which results in cushioning of the cavitation. This effect was studied by observing the effect on power output on water at different temperatures. Water (1250ml) was charged to the vessel, and after calibration at 20 °C, the probe was turned on for 10 mins. at power setting 5 at a depth of 7.1cm at 10 °C to 70 °C in steps of 10 °C. Graph 2.7 below shows a marked decrease in heat output from the probe as the temperature is increased. This effect is in strong agreement with the literature.

Graph 2.7 Temperature



2.8.5 COMPREHENSIVE SOLVENT STUDY

The earlier study into the various parameters that may effect ultrasonic output suggests that the vapour pressure of the solvent has a significant effect on the sonic output of the probe. Therefore several series of solvents were examined using the same methodology as detailed previously. The solvent (1250ml) was charged to the vessel, and after stabilisation at 20 °C, the reactor was calibrated. The solvents were then sonicated for ten minutes at a power setting of 5.

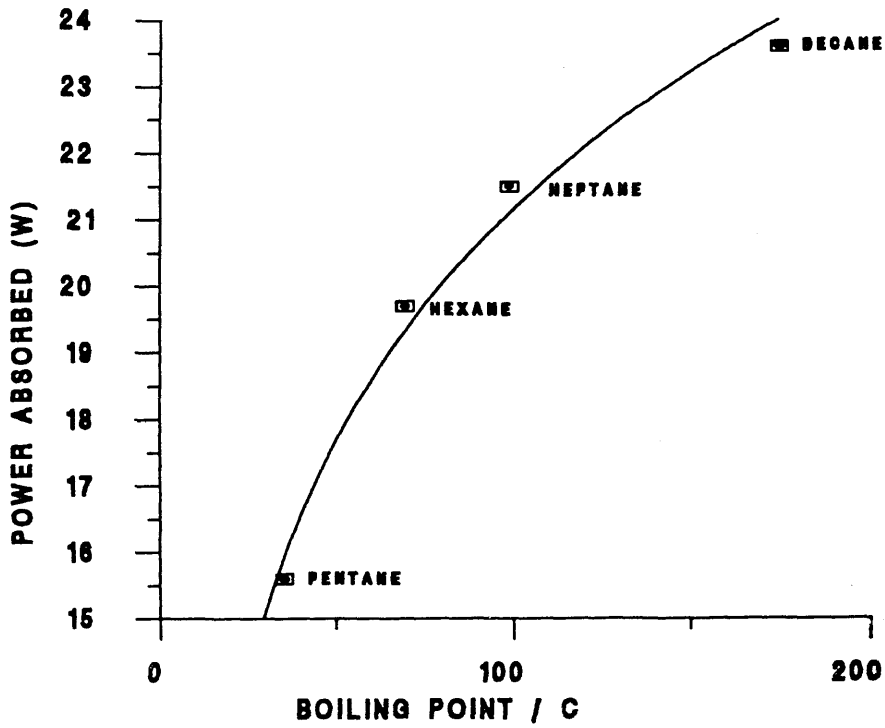
This second solvent study was carried out using a different sonic horn. The equipment and design were exactly the same, however the probe length was slightly longer. This enabled the probe to be exactly tuned to an optimum energy level, whereas the previous probe was slightly out of tune. This probe therefore gave a slightly higher output than before and the two sets of results can be compared. To enable the previous set of experiments to be used in conjunction with the more recent results a factor of 1.12 was used to calculate the power absorbed by thiophene and THF.

Solvent	Initial Values		New Values	
	Integral(kJ)	Av.(W)	Integral(kJ)	Av.(W)
Water	24.8	41.3	26.4	44.0
Butan-1-ol	22.5	37.5	26.2	43.6
Methanol	19.4	32.3	22.3	37.1
Toluene	21.5	35.8	24.1	40.1
Acetone	18.5	30.8	20.8	34.6
Thiophene	23.4	39.0	26.2*	43.7*
THF	20.8	34.7	23.3*	38.8*

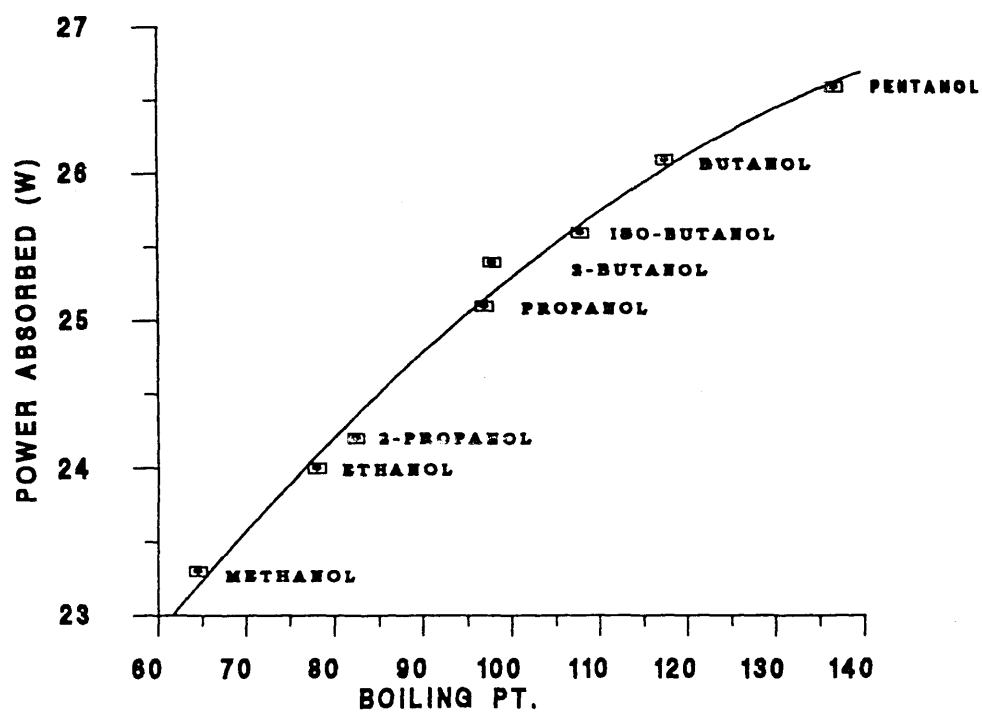
*-Calculated Values

As can be seen from the graphs each series of results shows strong evidence that as the boiling point of a series i.e. alkanes, alcohols and ketones is increased, the power absorbed by the solvent also increases (Graphs 2.8 - 2.12).

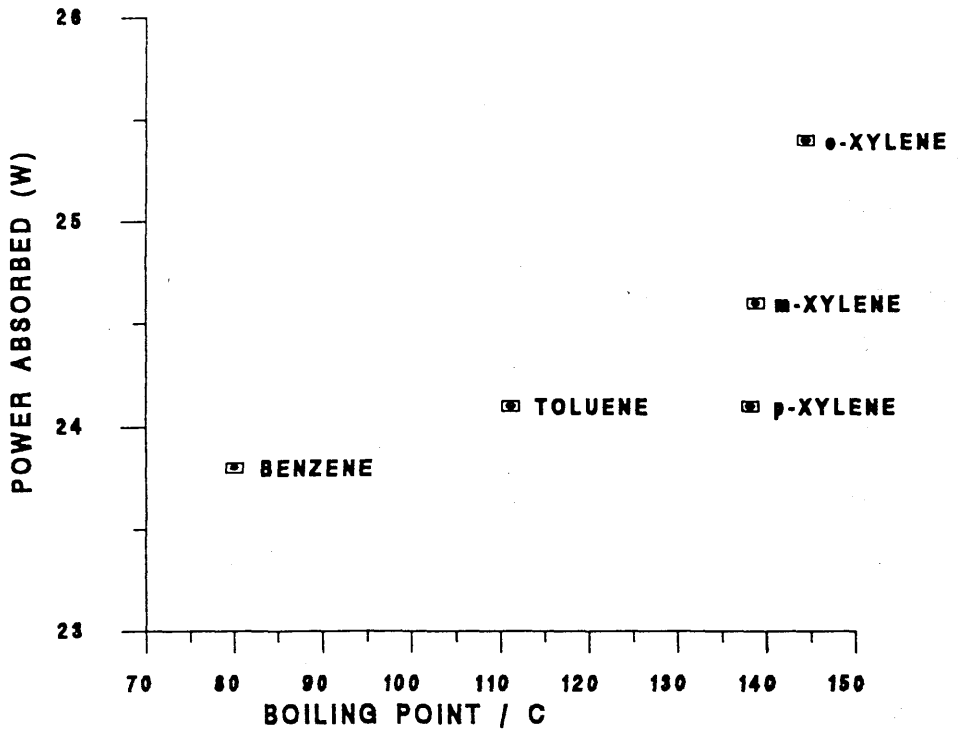
Graph 2.8 Alkane Series



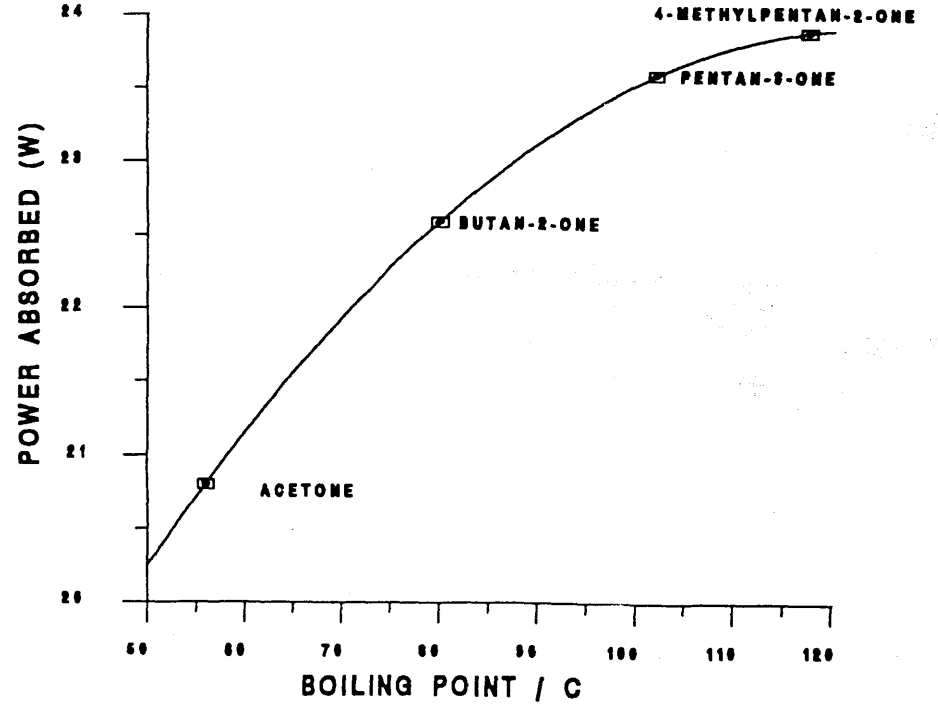
Graph 2.9 Alcohol Series



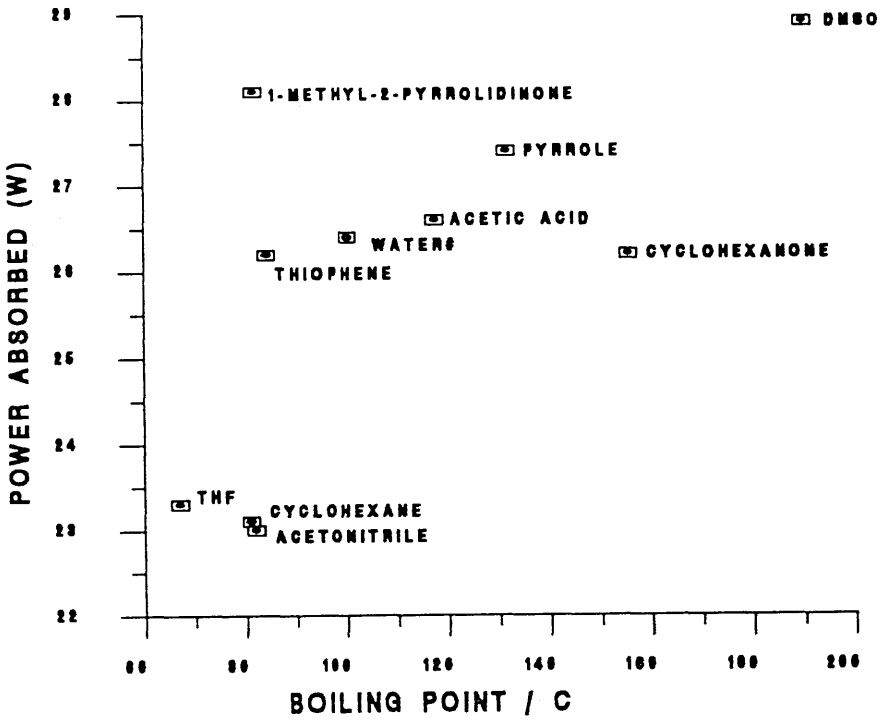
Graph 2.10 Aromatic Series



Graph 2.11 Ketone Series



Graph 2.12 Power Absorbed by Other Compounds



In all the solvent series, examined the power absorbed by the solvent was not a linear relationship; instead, the power output/boiling point ratio decreases slightly as the boiling point increases. There seems to be no relationship between the three series, however, the alcohols seem to absorb more energy than the compounds with the same number of carbons in the alkane series. This would suggest that the power absorbed may be influenced by the degree of hydrogen bonding within the solvent. This theory may also extend to the carbonyl compounds, when the ketones are compared to the alkanes, the ketones have a greater ability to absorb ultrasound. In the case of the aromatics (Graph 2.10) the curve is practically a straight line between benzene, toluene, and p-xylene indicating substitution has little effect on the benzene ring. However, when para-, meta-, and o-xylene are compared there is a marked difference between them implying that stoichiometry alters absorbance. The final graph (Graph 2.12) illustrates several other non-related solvents, there is a general trend of increased power absorbance with higher boiling point, but this is less well-defined compared to the related series.

Physical properties of the solvents are listed in appendix 1.

2.8.6 Overall Comments on the Calorimetry Study.

It should be noted that the ultrasonic generator has a power monitor which throughout the experiment gave a rough indication of how much power was being absorbed by the system. This can be used in conjunction with the power setting to maintain consistency between experiments.

Overall it can be seen that temperature, solvent, probe depth, and power setting all have an effect on the energy output that is transferred from the probe into the media surrounding it. Increasing the temperature decreases the power output; energy is available from along the length of the probe, not just from the tip; increasing the power setting gives a linear increase in power available to the system; and energy output is dependant on the solvent vapour pressure.

2.9.0 PROBE TIP WEAR

Calorimetry wear

In the calorimetry studies it was noticed a fine titanium dispersion had built up over the course of several runs that involved using the same solvent (water). This water was drained and filtered to yield 0.1g titanium metal from the tip. The diameter of the probe tip is 12mm, giving a surface area of 1.13cm^2 and a metal loss of approx.0.02$g/cm^2/hr$ at an equivalent power setting of 5.0.

Synthetic wear

In appendix 3 are photographs of three replaceable ultrasonic probe tips. The first is a new probe tip made by the mechanical engineers at the university and only machining marks are evident. The second photograph shows a probe tip that has been used for a variety of experiments and would be due for replacement if it was in use. This wear is caused by the intense cavitation at the surface of the metal causing it to erode. The third photograph shows a very worn tip. This tip resulted from extended use without checking the tip. This situation arose from the equipment being used by several people in a short space of time, and none checked the tip from wear. This is a very good example of cavitation erosion. The hemispherical pattern into the metal is particularly interesting.

3.0 EXPERIMENTAL

3.0 EXPERIMENTAL

Column chromatography was performed using pressurised short path columns of Merck Kieselgel 60. N.m.r spectra were recorded on a Bruker AC 200 spectrometer. Infrared spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrophotometer. Reactions were sonicated using a Sonics and Materials sonic probe model VC 600 fixed frequency 20 kHz, output 600 watts electrical, 100 watts ultrasonic. GC-MS analyses were carried out on a Hewlett Packard 5890 series II gas chromatograph, with a Hewlett Packard 5971A mass selective detector, and a Hewlett Packard Chemstation data processing system.

3.1.1 Coupling of pivalic acid - General Method Using 2 Equivalents of Fenton's reagent.

Note:- Yield is calculated on mass recovered.

Pivalic acid (10.2g, 0.1 mol), distilled water (170 ml) and conc. H_2SO_4 (2.0 ml) were placed in a 1 l beaker which was immersed in an ice/water bath to maintain the temperature below 35 °C. Iron (II) sulphate heptahydrate (56g, 0.2 mol) was dissolved in distilled water (200 ml) and conc. H_2SO_4 (12 ml), and placed in an addition funnel. Hydrogen peroxide (100 vol., 23 ml, 0.2 mol) was diluted with water (10 ml) and placed in a burette. These two solutions were added simultaneously and equivalently over 30 mins to the suspension of pivalic acid. The solution was either irradiated with ultrasound or stirred with an overhead stirrer during the addition. The ultrasonic probe was set at power level eight, and the overhead stirrer set at approx. 100 rpm.

After 30 minutes the aqueous suspension of organic products was extracted with ethyl acetate (3 x 100 ml), and the organic phase was washed with brine (3 x 150 ml), dried ($MgSO_4$), and the solvent evaporated *in vacuo* to yield a dark brown oil. Tlc (3:1 ethyl acetate:petroleum spirit) indicated a complex mixture, the mixed acids on the tlc plate were visualised by spraying the plate with neat universal indicator. The resulting mixture was subjected to short path pressurised column chromatography using gradient elution with 20% to 50% acetone/petroleum ether (60-80 °C). The least polar product eluted was identified as unreacted pivalic acid (sonicated 1.7g; stirred 4.0g). The next product obtained was the dimer, tetramethyladipic acid **(161)** (sonicated 3.1g, 30%; stirred 1.6g, 16%), m.p. 186-193°C, υ_{max} cm^{-1}(KBr) 3400-2500, 3000-2800, 1705, 1221, δ_H (CD_3COCD_3, 200 MHz) 1.16 (12H, 4 x $-CH_3$), 1.53 (4H, $-CH_2CH_2-$), δ_C (CD_3COCD_3, 50MHz), 25.40 (4 $-CH_3$), 36.28 (2 $-CH_2-$), 179.01 (2 -COOH), m/z 203 (protonated TMAA). Next, the trimer **(163)** was eluted (sonicated 3.0g, 30%; stirred 1.3g, 13%), m.p. 223-227 °C, $C_{15}H_{26}O_6$ requires

C, 59.6; H, 8.7% Found C, 59.6; H, 8.5%. υ_{max} cm^{-1} (KBr) 3400-2500, 3000-2800, 1692, 1230, δ_H (CD_3OD, 200 MHz) 1.09 (3H, s, CH_3), 1.15 (12H, 4 x CH_3), 1.38-1.60 (8H, m, 4 x CH_2) and 5.1 (3H, broad s, 3 x COOH), δ_C (CD_3COCD_3, 50MHz) 21.67 (CH_3), 25.4 (2 x CH_3), 25.7 (2 x CH_3), 35.0 (2 x CH_2), 36.2 (2 x CH_2), 42.7 (2 x C), 46.1 (C), 180.8 (COOH) and 181.7 (2 x COOH), m/z 303 ($M^{\cdot+}$+ H; 10%), 285 (23%), 257 (100%), 239 (95%), 221 (30%), 211 (50%).
Finally a mixture of tetramers (sonicated 3.2g; stirred 3.2g) was obtained as a foam, υ_{max} cm^{-1} (KBr) 3400-2500, 3000-2800, 1701 and 1230 cm^{-1}.

3.1.2 Coupling of Pivalic Acid Using High Shear Stirrer

The reaction was carried out as the general method, except the solution was stirred with a Greaves mixer Type GM-C at setting 22. Isolation of the products by column chromatography afforded TMAA (1.4g), a mixture of trimers and tetramers (4.1g), and recovered starting material (4.7g).

3.1.3 Crystallisation of Tetramethyladipic acid

Purification of TMAA was carried out by recrystallisation from pure acetone or ethanol.

Initial Equivalents Study

3.1.4 Coupling of Pivalic Acid with 3 Equivalents of Fenton's Reagent

Note:- The yield is calculated from here onwards with respect to the equivalents of Fenton's Reagent used.

The reaction was carried out as the general method (reaction 3.1.1) but with the following amounts of reactants: pivalic acid (10.2g, 0.1 mol) in water (170 ml) and conc. H_2SO_4 (2 ml); $FeSO_4.7H_2O$ (83.7g, 0.3 mol) in water (200 ml) and conc. H_2SO_4 (12 ml); H_2O_2 (100 vol, 34 ml, 0.3 mol). The resulting reaction mixture was subjected to short path pressurised column chromatography using gradient elution with 20% to 50% acetone/petroleum ether (60-80 °C). The sonicated reaction afforded TMAA (2.5g, 8%), a mixed fraction of trimers and tetramers (3.7g, 12%), and recovered starting material (1.0g). The stirred equivalent of the reaction afforded TMAA (0.7g, 2.3%), a mixed fraction of trimers and tetramers (4.0g, 13%), and recovered starting material (5.5g).

3.1.5 Coupling of Pivalic Acid with 1 Equivalent of Fenton's Reagent

The reaction was carried out as method 3.1.1 but with the following amounts of reactants: pivalic acid (10.2g, 0.1 mol) in water (170 ml) and conc. H_2SO_4 (2ml); $FeSO_4.7H_20$ (28g, 0.1mol) in water (200 ml) and conc. H_2SO_4 (12 ml); H_2O_2 (100 vol, 5.75 ml, 0.1 mol). The sonicated reaction afforded TMAA (2.25g, 33%), a mixed fraction of trimers and tetramers (2.25g, 22%), and the remainder consisting of recovered starting material (3.4g). The stirred equivalent afforded TMAA (2.25g, 22%), a mixed fraction of trimers and tetramers (2.24g, 22%), and recovered starting material (3.4 g).

Table 3.1

(TMAA Yield (%) Based on Fenton's Reagent)

	Yield			
	SONICATED		STIRRED	
Equivs	TMAA	Oligomers	TMAA	Oligomers
1	2.25g, 22%	2.24g, 22%	2.0g, 20%	2.25g, 23%
2	3.3g, 16%	3.7g, 18%	1.4g, 7%	5.35g, 26%
3	2.5g, 8%	3.7g, 12%	0.7g, 2%	4.0g, 13%

Initial Effect of Dissolved Gases

3.1.6 Coupling of Pivalic Acid Using Modified Reaction Flask

This method is the same as the general method except it is one quarter the scale, and is carried out in the modified reaction flask which will now be referred to as the US (ultrasonic) flask. This flask could be sealed to allow a blanket gas (e.g. nitrogen) to be introduced. To the flask was added pivalic acid (2.55g, 0.025 mol) in water (42.5 ml) and conc. H_2SO_4 (2 ml). Two addition funnels were attached to the flask and one filled with $FeSO_4.7H_20$ (14g, 0.05 mol) dissolved in water (50ml) and conc H_2SO_4 (3 ml), to the other was added H_2O_2 (100vol, 5.75ml, 0.05 mol). The appropriate gas (N_2, Ar, O_2) was bubbled through the solution before (15 mins) and during the reaction. The solution was kept below 35 °C using an ice/salt/water bath. The flask was fitted with the US probe or overhead stirrer as required.

After 30 minutes the aqueous suspension of organic products was extracted with ethyl acetate (3 x 50 ml) and the organic phase washed with brine (3 x 50 ml), dried ($MgSO_4$), and the solvent evaporated *in vacuo*. The work up was identical method 3.1.1. The yields of TMAA and oligomers were calculated based on the amount of Fenton's reagent used.

Table 3.2

Effect of Dissolved Gas on Yield of TMAA (%)

	SONICATED		STIRRED	
	TMAA	OLIG	TMAA	OLIG
AIR	0.65g, 13%	0.65g, 13%	0.27g, 6%	1.02g, 20%
ARGON	0.47g, 9%	1.03g, 21%	0.28g, 6%	0.82g, 16%
NITROGEN	0.80g, 16%	0.54g, 11%	0.26g, 6%	0.82g, 16%

Second Equivalent Study

Coupling of Pivalic Acid

These reactions were carried out under nitrogen as per the method outlined for the US flask (Method 3.1.6)except for the following amounts of reagents:

3.1.7 2 Equivalents

Pivalic acid (2.55g, 0.025 mol) in water (42.5 ml) and conc. H_2SO_4 (0.5 ml). $FeSO_4.7H_2O$ (14g, 0.05 mol) in water (50 ml) and conc. H_2SO_4 (3 ml). H_2O_2 (100 vol, 5.75 ml, 0.05 mol).

3.1.8 1 Equivalent

Pivalic acid (2.55g, 0.025 mol) in water (42.5 ml) and conc. H_2SO_4 (0.5 ml). $FeSO_4.7H_2O$ (7g, 0.025 mol) in water (50 ml) and conc. H_2SO_4 (3 ml). H_2O_2 (100 vol, 2.9 ml, 0.025 mol) diluted with water (2.85 ml).

3.1.9 0.5 Equivalents

Pivalic acid (5.1g, 0.05 mol) in water (85 ml) and conc. H_2SO_4 (1.0 ml). $FeSO_4.7H_2O$ (7g, 0.025 mol) in water (50 ml) and conc. H_2SO_4 (3 ml). H_2O_2 (100 vol, 2.9 ml, 0.025 mol) diluted with water (2.85 ml).

3.1.10 0.33 Equivalents

Pivalic acid (7.65g, 0.075 mol) in water (127.5 ml) and conc. H_2SO_4 (1.5 ml). $FeSO_4.7H_2O$ (7g, 0.025 mol) in water (50 ml) and conc. H_2SO_4 (3 ml). H_2O_2 (100 vol, 2.9 ml, 0.025 mol) diluted with water (2.85 ml).

3.1.11 0.167 Equivalents

Pivalic acid (7.65g, 0.075 mol) in water (127.5 ml) and conc. H_2SO_4 (1.5 ml). $FeSO_4.7H_2O$ (3.5g, 0.0125 mol) in water (50 ml) and conc. H_2SO_4 (3 ml). H_2O_2 (100 vol, 1.45 ml, 0.0125 mol) was diluted with water (4.30 ml).

3.1.12 0.167 Equivalents - High Concentration of Starting Material

Pivalic acid (7.65g, 0.075 mol) in water (42.5 ml) and conc. H_2SO_4 (0.5 ml). $FeSO_4.7H_2O$ (3.5g, 0.0125 mol) in water (50 ml) and conc. H_2SO_4 (3 ml). H_2O_2 (100 vol, 1.45 ml, 0.0125 mol) was diluted with water (4.30 ml).

Table 3.3

Effect of Number of Equivalents on Yield of TMAA(%)

	Yield			
	Sonicated		Stirred	
Equivs.	TMAA	OLIG	TMAA	OLIG
2	0.35g, 14%	0.28g, 11%	0.24g, 5%	0.82g, 16%
1	0.66g, 26%	0.70g, 28%	0.28g, 11%	0.91g, 36%
0.5	0.84g, 34%	0.55g, 22%	0.84g, 34%	0.44g, 18%
0.33	1.53g, 61%	trace, < 5%	1.29g, 55%	trace, .<5%
0.167	0.76g, 60%	trace, <5%	0.90g, 71%	trace, <5%

Main Study

3.1.13 Coupling of Pivalic Acid with High (0.33) Equivalents of Fenton's Reagent with Low Dilution

The reaction was carried out in US flask with the appropriate gas being bubbled through the solutions and with the following amounts of reactants: pivalic acid (2.55g, 0.025 mol) in water (42.5 ml) and conc. H_2SO_4 (0.5 ml). $FeSO_4.7H_2O$ (2.33g, 0.0083 mol) in water (25 ml) and conc. H_2SO_4 (1.5 ml) and H_2O_2 (100 vol, 0.97 ml, 0.0083 mol) diluted to 6.0 ml with water. The excess pivalic acid was azeotroped with water to isolate the TMAA.

3.1.14 Coupling of Pivalic Acid with Low Equivalents of Fenton's Reagent with Low Dilution

The reaction was carried out as method 3.1.13 but with the following amounts of reactants: pivalic acid (2.55g, 0.025 mol) in water (42.5 ml) and conc. H_2SO_4 (0.5 ml). $FeSO_4.7H_2O$ (1.165g, 0.0042 mol) in water (25 ml) and conc. H_2SO_4 (1.5 ml) and H_2O_2 (100 vol, 0.485 ml, 0.0042 mol) diluted to 6.0 ml with water. The excess pivalic acid was azeotroped with water to isolate the TMAA.

3.1.15 Coupling of Pivalic Acid with High Equivalents of Fenton's Reagent with High Dilution

The reaction was carried out as reaction 3.1.13 but with the following amounts of reactants: pivalic acid (1.275g, 0.0125 mol) in water (42.5 ml) and conc. H_2SO_4 (0.5 ml). $FeSO_4.7H_2O$ (1.165g, 0.0042 mol) in water (25 ml) and conc. H_2SO_4 (1.5 ml) and H_2O_2 (100 vol, 0.485 ml, 0.0042 mol) diluted to 6.0 ml with water. The excess pivalic acid was azeotroped with water to isolate the TMAA.

3.1.16 Coupling of Pivalic Acid with Low Equivalents of Fenton's Reagent with High Dilution

The reaction was carried out as above but with the following amounts of reactants: pivalic acid (1.275g, 0.0125 mol) in water (42.5 ml) and conc. H_2SO_4 (0.5 ml). $FeSO_4.7H_2O$ (0.582g, 0.0021 mol) in water (25 ml) and conc. H_2SO_4 (1.5 ml) and H_2O_2 (100 vol, 0.24 ml, 0.0021 mol) diluted to 6.0 ml with water. The excess pivalic acid was azeotroped with water to isolate the TMAA.

Table 3.4

			% Yield of TMAA		
Equiv.	Dil.	US.	Ar	O_2	N_2
0.33	low	on	0.45, 54	0.27, 33	0.38, 63
0.33	low	on	0.45, 54	0.30, 36	0.50, 60
0.17	low	on	0.20, 48	0.08, 21	0.32, 76
0.17	low	on	0.19, 45	0.08, 19	0.30, 71
0.33	high	on	0.16, 37	0.11, 26	0.27, 64
0.33	high	on	0.14, 33	0.11, 26	0.24, 57
0.17	high	on	0.12, 57	0.06, 29	0.14, 67
0.17	high	on	0.12, 57	0.05, 24	0.14, 67
0.33	low	off	0.50, 60	0.24, 29	0.50, 60
0.33	low	off	0.46, 55	0.27, 32	0.56, 67
0.17	low	off	0.27, 64	0.20, 47	0.34, 80
0.17	low	off	0.28, 67	0.17, 51	0.35, 83
0.33	high	off	0.24, 57	0.18, 45	0.31, 74
0.33	high	off	0.21, 60	0.19, 43	0.28, 67
0.17	high	off	0.17, 40	0, 0	0.17, 81
0.17	high	off	0.15, 36	0, 0	0.18, 86

Follow-up Study; Coupling of Pivalic Acid Under High Dilution, Nitrogen, with Mechanical Stirring

Conditions as stated in reaction 3.1.16 except the molar equivalents of Fenton's reagent below.

3.1.17 0.080 Equivalents

Pivalic acid (1.275g, 0.0125 mol) in water (42.5 ml) and conc. H_2SO_4 (0.5 ml). $FeSO_4.7H_2O$ (0.279g, 0.0010 mol) in water (25 ml) and conc. H_2SO_4 (1.5 ml). H_2O_2 (100 vol, 0.11 ml, 0.0010 mol) diluted with water (5.89 ml).

3.1.18 0.167 Equivalents

See reaction 3.1.16.

3.1.19 0.20 Equivalent

Pivalic acid (1.275g, 0.0125 mol) in water (42.5 ml) and conc. H_2SO_4 (0.5 ml). $FeSO_4.7H_2O$ (0.697g, 0.0025 mol) in water (25 ml) and conc. H_2SO_4 (1.5 ml). H_2O_2 (100 vol, 0.29 ml, 0.0025 mol) diluted with water (5.71 ml).

3.1.20 0.24 Equivalents

Pivalic acid (1.275g, 0.0125 mol) in water (42.5 ml) and conc. H_2SO_4 (0.5 ml). $FeSO_4.7H_2O$ (0.836g, 0.0030 mol) in water (25 ml) and conc. H_2SO_4 (1.5 ml). H_2O_2 (100 vol, 0.34 ml, 0.0030 mol) diluted with water (5.66 ml).

3.1.21 0.28 Equivalents

Pivalic acid (1.275g, 0.0125 mol) in water (42.5 ml) and conc. H_2SO_4 (0.5 ml). $FeSO_4.7H_2O$ (0.976g, 0.0035 mol) in water (25 ml) and conc. H_2SO_4 (1.5 ml). H_2O_2 (100 vol, 0.40 ml, 0.0035 mol) diluted with water (5.60 ml).

3.1.22 0.33 Equivalents

See reaction 3.1.15.

Table 3.5

Equiv.	g,% Yield	Ave
0.080	0.10, 98	98
0.080	0.10, 98	
0.167	0.19, 90	87
0.167	0.18, 84	
0.200	0.25, 84	80
0.220	0.25, 76	
0.240	0.22, 73	70
0.240	0.20, 66	
0.280	0.24, 68	69
0.280	0.25, 71	
0.330	0.27, 64	67
0.330	0.30, 71	

3.1.23 Coupling of Pivalic Acid with Fenton's Reagent[330]

As per the experimental method described in the literature[329]; Pivalic acid (10.2g, 0.10 mol), distilled water (120 ml) and conc. H_2SO_4 (1.5 ml) were added to a 500ml three necked round bottomed flask. This mixture was stirred with an overhead stirrer in an ice bath until the temperature reached 10 °C. Two addition funnels were fitted to the flask and one charged with H_2O_2 (100 vol, 11.5 ml, 0.10 mol), and the other with $FeSO_4.7H_2O$ (27.9g, 0.10 mol) dissolved in water (57.5 ml) and conc. H_2SO_4 (5.5 ml). These solutions were added simultaneously and equivalently over a 15

minute duration. The final temperature of the solution was 20 °C. Once addition was complete the flask was fitted with a heating mantle and condenser. Approximately 100 ml of water and pivalic acid mixture were azeotroped off. The mixture was stirred throughout the distillation and subsequent cooling. the remaining organic matter was filtered off, washed with water and dried (3.6g). The crude product was then dissolved in ammonia solution (0.88 S.G., 10 ml) and water (5 ml), then filtered to remove iron precipitate. The ammonia was boiled off, water added (150 ml), then the acid was precipitated by adding conc. HCl (approx. 5 ml). This gave the refined product (2.9g). Additionally to this method, the aqueous phase of the reaction mixture was subjected to solvent extraction with ethyl acetate (3 x 100 ml), washed with brine (3 x 100 ml), dried ($MgSO_4$) and the solvent removed *in vacuo*, to yield further organics (1.3g). Tlc (3:1 ethyl acetate:petroleum spirit (60-80 °C)) of the precipitated acid indicated no pivalic acid was present. The solid obtained was impure with several products evident. Tlc of the extract indicated it was mainly pivalic acid, clearly indicating the aqueous solubility of the acid. The combined products were subjected to short path pressurised column chromatography using gradient elution with 20% to 50% acetone/petroleum ether (60-80 °C). The least polar product eluted was the dimer (2.0g) tetramethyladipic acid, followed by the trimer plus mixed tetramers (1.45g). An ethanol strip afforded baseline products (0.8g).

3.1.24 Coupling of Pivalic Acid using Fenton's Reagent - Method Supplied by Shell Research Bv.

Pivalic acid (10.2g, 0.1 mol), distilled water (20 ml), and conc. H_2SO_4 (1 ml) were added to a 250ml three necked round bottomed flask. The mixture was vigorously stirred with an overhead stirrer while the flask equilibrated in a water bath at 45 °C. Two addition funnels were fitted to the flask and one filled with $FeSO_4.7H_2O$ (27.9g, 0.1 mol) dissolved in 3N H_2SO_4 (60 ml, 8.8g H_2SO_4, made up to 60 ml with water), and the other with H_2O_2 (100 vol, 11.3g, 0.10 mol) diluted to 15 ml with water. Whilst rapidly stirring the solution the reagents were added continuously over one hour, at the end of which the reaction mixture was still at 45 °C. After the addition the remaining pivalic acid was azeotroped out of solution with water under vacuum until none remained (75 °C, approx 30mm Hg). Hot water (50 ml) was added and the solution and semi-solid mass was washed for 10 minutes at 80 °C. The aqueous phase was decanted off, and the washing procedure repeated with fresh water. The crude product was isolated by filtration (1.3g). In addition to the method supplied the washings were extracted with ethyl acetate (3 x 50 ml), dried ($MgSO_4$), and the

solvent removed *in vacuo* to produce organics (3.2g). Tlc (3:1 ethyl acetate: petroleum ether (60-80 °C)) indicated mixed acids with the major spot corresponding to tetramethyladipic acid.
This experiment was repeated except at the end of the addition the pivalic acid was azeotroped out of the reaction mixture, then the remaining organics were extracted with ethyl acetate (3 x 50 ml), washed with brine (3 x 50 ml), dried ($MgSO_4$), and the solvent removed *in vacuo*, to give a semi-solid mass (2.40g). Tlc indicated mixed products, which were separated using short path column chromatography with gradient elution 20 to 50% acetone/petroleum ether (60 - 80 °C). This separated the dimer (0.92g) and a mixed fraction of trimers and mixed tetramers (1.47g).

3.1.25 Isolation of Tetramers from Previously Produced Baseline Material

From previous columns a small amount of polar material, compound "D", thought to be tetramers, had been isolated (50 mg). D was subjected to tlc (50:50 ethanol: petroleum spirit (60 - 80 °C) and run against ethanol strip baseline material obtained from pivalic acid coupling reaction mixtures. The baseline material was found to have a large majority of compound D within.

The following solvents were unsuccessful in recrystallising the acid: ethanol, methanol, methyl ethyl ketone, acetic acid, acetone. They either dissolved the acid completely, or did not dissolve all of it.

Alternatives

a) The baseline material (2.0g) was dissolved in refluxing MEK (20 ml)/Methanol (15 ml)/acetic acid (5 ml), cooled in an ice/salt bath, then diethyl ether (15 ml) was added to precipitate the acid. This was filtered to yield a semi-solid, which was washed with ethanol to afford tan coloured "crystals" (0.3g).

b) The baseline material (2.0g) was dissolved in aqueous sodium hydroxide (2M, 50 ml). This was extracted with diethyl ether (3 x 30 ml) to remove insoluble organic matter (neutral or basic). The acid in the aqueous phase was precipitated by acidifying with dil. HCl. The precipitate was then extracted with diethyl ether (4 x 30 ml), washed with brine (3 x 30 ml), charcoal (0.2g) was added and filtered out, dried ($MgSO_4$), then the solvent removed *in vacuo*, to yield a white foam (0.85g).

c) The baseline material (2.0g) was dissolved in ammonia (1N, 100 ml) and heated to 80 °C, then slightly more than an equal volume of formic acid (1N) was added. The mixture was allowed to cool and left for 48hrs, after which time the acid had not crystallised. Dil. HCl was added to precipitate the acid out of solution. This produced an unsatisfactory brown non-crystalline mixed product (1.5g).

3.1.26 Sonication of Pivalic Acid and Water

a) Pivalic acid (2.55g, 0.025 mol) was suspended in water (100ml) in a 250ml conical flask. This was immersed in a Kerry ultrasonic cleaning bath with the bottom of the flask set at 3cm from the floor of the tank. The height was set by previously sonicating a piece of aluminium foil, and observing where maximum pitting (cavitation) occurred (4.5 cm from the floor). The flask was then sonicated for 9 hours, after which time the organics were extracted with ethyl acetate (3 x 50 ml), washed with brine (2 x 50 ml), dried ($MgSO_4$), and the solvent removed *in vacuo*. Tlc (3:1 ethyl acetate: petroleum spirit (60-80 °C)) indicated only starting material present.

b) Supplementary to the Kerry ultrasonic bath, pivalic acid (15g, 0.15mol) and water (200ml) were placed in a 1 litre beaker and sonicated with the ultrasonic horn for 2 hours at full power. Work up and tlc as above indicated only starting material present.

3.1.27 Sonication of Pivalic Acid/Water/and Hydrogen Peroxide

Pivalic acid (2.55g, 0.025 mol) and water (42.5 ml) were charged to the ultrasonic reaction vessel. Whilst irradiating the solution with ultrasound (PS=8) and cooling the reaction vessel with an ice/water bath to maintain the temperature below 30 °C, hydrogen peroxide (100 vol, 2.9 ml, 0.025 mol) was added continually over 30 minutes. The organics were extracted with ethyl acetate (3 x 50 ml), washed with brine (2 x 50 ml), dried ($MgSO_4$), and the solvent removed *in vacuo*. Tlc (3:1 ethyl acetate: petroleum spirit (60-80 °C)) indicated only starting material present.

3.1.28 HPLC Method for Analysis of Pivalic Acid Coupling Reaction Mixture

The following conditions were the best obtained for analysing the percentage mass of pivalic acid, tetramethyladipic acid and to a certain extent the trimer acid, but not the tetramer fraction.

Equipment

Pump, Spectra-Physics SP880 LC; Detector, Hewlett-Packard HP 1050 series multiple wavelength detector; Integrator, Hewlett-Packard HP3396 series II integrator; Column, C_8 reverse phase; Eluant, degassed 0.2M Na_2HPO_4 (28.4g/l) buffered to pH 8 with H_3PO_4.

Settings

Pump, max psi=2500, flow=1.40, psi=1900; Detector, wavelength 217 nm, band width 4, reference wavelength 350 nm, band width 40 nm; Integrator attenuation 1, chart speed 0.5, threshold 3, peak width 0.10; Timetable, 2.300 INTG No.= 4, 3.000 INTG No.= -4, 5.000 PK WD = 0.50, 10.000 PK WD = 0.80, 23.000 PK WD = 2.00.

Calibration of Integrator

An internal integration table was constructed using mixed standards. Compounds A (pivalic acid), B (dimer - tetramethyladipic acid), C (trimer), D (tetramers) were dissolved together in the buffer (100.0 ml) to known concentrations: 0.10%, 0.05%, 0.025%, 0.010%. These standards were then used to produce calibration curves for each compound within the integrator, which was then programmed to automatically calculate the concentrations of the samples.

Retention Times

Pivalic acid 8.28 min., TMAA 17.32 min., trimer 30.92 min., tetramers 1.9 - 2.6 min. (broad).

Unfortunately reproducible results could only be obtained for pivalic acid and its dimer TMAA.

3.1.29 Methyl Esterification of Tetramethyladipic acid.

TMAA (1.0g, 0.005 mol) was dissolved in methanol (100 ml) and conc. H_2SO_4 (2 ml) was added. The solution was then refluxed for 18 hrs. after which time tlc (3:1 ethyl acetate: petroleum spirit (60-80 °C)) indicated that no starting material remained. Half of the methanol was evaporated off *in vacuo* and the remaining solution was poured onto ice/water which precipitated the product. The damp product was left overnight in a vacuum oven to dry. The crude product was recrystallised from water/methanol to yield the diester (0.6g, 53%). m.p. 45-46 °C, υ_{max} cm^{-1} (KBr) 3000-2800 (alkyl, C-H str.), 1727 (ester, C=O str.), 1200 (ester, C-O str.).

3.1.30 Methyl Esterification of Tetramethyladipic Acid

Tetramethyladipic acid (0.5g, 0.0025 mol), BF_3/methanol complex (14%, 25 ml) were placed in a round bottomed flask (50 ml) and heated to reflux. After 10 mins, tlc (3:1 ethyl acetate: petroleum spirit (60-80 °C)) indicated starting material still remained, reflux was continued for further 20mins at which time tlc indicated no starting material remained. The solvent was removed *in vacuo* and the product redissolved in ethyl acetate (40 ml), washed with sodium bicarbonate solution (25 ml), brine (2 x 25 ml), dried ($MgSO_4$), and the solvent evaporated *in vacuo* to yield the product (0.3g), m.p. 43-45 °C.

3.1.31 Methyl Esterification of Baseline Products Isolated from Coupling of Pivalic Acid Reaction Mixture

Baseline material (3.4g) was dissolved in methanol (100 ml) and refluxed with sulphuric acid (1 ml) for 19 hrs. Tlc indicated most of the starting material had reacted. Half of the methanol was evaporated *in vacuo*. The remaining solution was poured onto ice/water to precipitate the product. The product was a non-crystalline syrup, it was therefore dissolved in ethyl acetate, washed with sodium bicarbonate, brine, dried ($MgSO_4$), and the solvent evaporated *in vacuo*. This gave a very poor yield (0.3g). Due to the low yield obtained this reaction was not investigated further.

3.1.32 Esterification of Pivalic Acid Coupling Reaction Mixture (3.1.1)

The reaction mixture (6.5g) of the above (experiment 3.1.1) was dissolved in methanol (300 ml) and conc. H_2SO_4 (1 ml), and refluxed for 8 hrs. The methanol was evaporated *in vacuo* and the resulting product dissolved in ethyl acetate (150 ml). The solution was then washed with brine (3 x 150 ml), dried ($MgSO_4$), and the solvent evaporated *in vacuo* to yield a brown syrup (1.8g).

3.1.33 Acid Chloride Preparation from Tetramethyladipic Acid

Tetramethyladipic acid (2.02g, 0.01 mol), 1,2-dichloroethane (18 ml), and phase transfer catalyst $BnEt_3NBr$ (0.0041g, 0.015 mmol) were added to a dry 50 ml round bottomed flask equiped with magnetic stirrer. The slurry was brought to reflux and thionyl chloride (1.54g, 0.021 mol) was added dropwise over 5 minutes, reflux was maintained for 84 hours. Tlc (3:1 ethyl acetate: petroleum ether) indicated that most of the starting material had reacted. I.R indicated that an acid chloride was present and little acid remained, υ_{max} cm^{-1}, 3000-2800 (alkyl, C-H str.), 1795 (alkanoyl chloride, C=O str.). The reflux was stopped and the solvent removed *in vacuo,* and remaining thionyl chloride was azeotroped off with toluene.

3.1.34 Methylation of Tetramethyladipicdiacetyl Chloride

The acid chloride prepared above was dissolved in toluene (10 ml). This solution was then dripped into stirred methanol (10 ml) contained in a 50ml round bottomed flask. After 2 hours no reaction had occurred. The flask was fitted with a condenser and heated to reflux for 24 hours. The solvent was evaporated *in vacuo*, then the reaction mixture was dissolved in ethyl acetate (25 ml), washed with sodium metabisulphite (50 ml) to remove any acid, washed with brine (3 x 50 ml), dried ($MgSO_4$), and the solvent removed *in vacuo* to yield crystals of the ester (0.6g), m.p. 41-44 °C, υ_{max} cm^{-1} (KBr) 3000-2800 (alkyl, C-H str.), 1727 (ester, C=0 str.), 1200 (ester , C-O str.)

3.1.35 Diazomethane Methyl Esterification of Tetramethyladipic Acid Using the Aldrich MNNG - Diazomethane Kit

Diazomethane Generation

N-methyl-N'-nitro-N-nitrosoguanidine (0.147g, 1 mmol) was transferred into the inner tube of the Aldrich apparatus. Diethyl ether (3 ml) was placed in the outer tube and the apparatus was assembled using the clamp provided with the kit. Distilled water (0.5 ml) was added to the inner tube using a syringe, and the whole apparatus placed in an ice bath behind a safety screen. NaOH solution (5N, 0.6 ml) was injected through the Teflon rubber septum via a syringe (1 ml) with a narrow gauge (No 22) needle tip prevent leakage around the shank. The injection of the sodium hydroxide was done at a rate of one drop per second. The mixture was shaken gently to ensure all the MNNG was reacting, and the reaction was left for 1 hour to ensure the diazomethane dissolved into the ether.

Esterification

TMAA (0.101g, 0.5 mmol) and ethanol (10 ml) were placed in a boiling tube and shaken to dissolve all the acid. The diazomethane solution prepared earlier was added to this, shaken and left for 1/2 hour. The diazomethane equipment was washed out with 25% glacial acetic acid solution to destroy any remaining diazomethane. The ethanol was evaporated *in vacuo* and the reaction mixture redissolved in ethyl acetate (10 ml), washed with sodium metabisulphite (2 x 10 ml), brine (2 x 10 ml), dried ($MgSO_4$), and the solvent evaporated *in vacuo*. There was no yield of ester. The reaction was repeated with the starting material suspended in ether in the apparatus and worked up as above, but again no measurable amount of ester was produced.

3.1.36 Coupling of Versatic 7 Acid (2-ethyl-2-methylbutanoic acid) "Pitchfork Acid", Stirred and Sonicated

Versatic 7 acid (3.25g, 0.025 mol), water (42.5 ml) and conc. H_2SO_4 (0.5 ml) were charged to the US flask. This was immersed in an ice/water bath until the temperature reached 10 °C, during which time (15 mins) nitrogen was bubbled through the solution. The flask was fitted with two addition funnels and one charged with $FeSO_4.7H_2O$ (14g, 0.05 mol) dissolved in water (50 ml) and conc. H_2SO_4 (3 ml). To the other was added H_2O_2 (100 vol, 5.75 ml, 0.05 mol). The two solutions were added simultaneously over 30 minutes while the solution was stirred or sonicated (PS=8). The solution was extracted with ethyl acetate (2 x 50 ml), washed with brine (3 x 50 ml), dried ($MgSO_4$), and the solvent removed *in vacuo*. Tlc (3:1 ethyl acetate: petroleum spirit (60-80 °C)) indicated mixed products in both reaction mixtures. The fractions were separated using column chromatography with gradient elution 20-50% acetone/ petroleum spirit (60-80 °C) to afford starting material (1.6g, ultrasound) (1.3g, stirred), B (0.4g, ultrasound) (0.4g, stirred), C & D (1.2g, ultrasound) (1.04g, stirred).

3.1.37 Coupling of Versatic 6 Acid, non-Sonicated

Method identical to method 3.1.25 except versatic 6 acid was used (2,2-dimethylbutyric acid) (11.6g, 0.1 mol). After addition the organics were extracted with ethyl acetate (3 x 100ml), dried ($MgSO_4$), and solvent removed *in vacuo*. Tlc indicated no reaction had occurred.

3.1.38 Coupling of Versatic 6 Acid with PTC, non-Sonicated

Method identical to reaction 3.1.37 except Aliquat phase transfer catalyst was added (1.0ml) to the reaction solution. After work up tlc indicated no reaction had occurred.

3.1.39 Coupling of Versatic 6 Acid, Sonicated

Versatic 6 acid (11.6g, 0.1 mol) was placed in a 700 ml reaction vessel along with water (400 ml) and conc. H_2SO_4 (3 ml). This was stirred in an ice bath to cool the liquid (12.5 °C). Whilst stirring the vessel with a magnetic stirrer solutions A & B were added continuously over 30 minutes, while irradiating the reaction vessel with ultrasound supplied from a sonic probe with fitted extender. Solution A: H_2O_2 (11.5 ml 100 vol, 0.10 mol) solution. B: $FeSO_4.7H_2O$ (27.9g, 0.10 mol) in water (57 ml) and conc. H_2SO_4 (5.5 ml). The organics were extracted with ethyl acetate (3 x 75 ml), dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The product appeared as a solid suspended in unreacted starting material. Therefore the starting material was

dissolved in the minimum amount of ethyl acetate and the product (360 mg) filtered off. m.p. >330 °C, υ_{max} cm^{-1} (KBr) 3500-2500 (carboxylic acid, O-H str.), 3000-2800 (alkyl, C-H str.), 1696 (carboxylic acid, C=O).

3.1.40 Coupling of t-Butanol, without Ultrasound

Tertiary butyl alcohol (90 ml, 70.2g, 0.947 mol) was dissolved in a solution prepared by mixing conc. H_2SO_4 (3.0 ml, 0.05 mol) with water (150 ml) in a round bottomed flask (500 ml), equipped with thermometer, magnetic stirrer, and two addition burettes. One burette was charged with hydrogen peroxide (100 vol, 11.5 ml, 0.10 mol), and the other with a solution of $FeSO_4.7H_2O$ (27.9g, 0.10 mol) and conc. H_2SO_4 (5.5 ml, 0.1 mol) in water (57 ml). The reaction vessel was immersed in an ice bath and was cooled to below 10 °C with stirring. The two solutions were then added simultaneously and equivalently over a period of 20 minutes, after which time the temperature had risen to 17 °C. When the addition was complete, 52% sodium hydroxide (5 ml, 0.1 mol) was added, followed by anhydrous sodium sulphate (25g). The solution was transferred to a separating funnel, t-butanol added (50 ml) and the organics extracted. The organic phase was neutralised with 52% sodium hydroxide and the aqueous precipitate returned to the original aqueous phase. The whole extraction process was repeated another three times and the organic phases combined. The solvent was distilled off under reduced pressure, until the temperature of the flask was 31.5 °C/ 0.7mm Hg. Ether extraction (4 x 50 ml) of the residue left in the flask after the solvent was removed produced damp yellow crystals (5.0g). Recrystallisation was attempted using ethyl acetate, cyclohexane, and water but all were unsuccessful. The crude product was extracted with cyclohexane/ether (30%) overnight then filtered off. The pale yellow crystals (3.7g) were then dissolved in a little water (10 ml), then the product was extracted using diethyl ether (4 x 50 ml), dried ($MgSO_4$), decolourised with charcoal, and after filtration the ether was evaporated *in vacuo*, to yield off white crystals (2.7g, 50% yield, based on moles peroxide used), m.p. 87-88.5 °C, υ_{max} cm^{-1} (KBr), 3500-3000 (alcohol, O-H str.), 3000-2800 (alkyl, C-H str.), 1379 & 1145 (3° alcohol, C-O str. & O-H def.).

3.1.41 Coupling of t-Butanol using Ultrasound.

Method and work-up were identical to above except the solution was irradiated with ultrasound. This produced no measurable increase in the yield of the dimer over the non-sonicated reaction.

3.2.1 Preparation of N-Hydroxypyridine-2-thione from its Sodium Salt

N-Hydroxypyridine-2-thione (NHPT) is supplied as its sodium salt in 40% aqueous solution. The sodium salt solution (50g) was diluted with water (20 ml), and conc. HCl (15 ml) added dropwise to precipitate the free acid, which was filtered and recrystallised from ethanol to yield an off-white crystalline solid (14.7g). This was recrystallised from ethanol once more, and any remaining solvent was removed in a vacuum oven (60 mm Hg, 40 °C), m.p. 70-72 °C).

3.2.2 Sonication of N-Hydroxypyridine-2-thione

NHPT (635 mg, 5 mmol) and benzene (50 ml) were charged to the US flask under argon, with ice/water cooling. This solution was sonicated (PS=5) for 3 hours at 30 °C, the flask was covered with aluminium foil to eliminate light. Tlc (50:50 ethyl acetate: petroleum spirit (60-80 °C)) indicated the majority of starting material was unreacted, but a small amount of unknown product was evident. The reaction mixture was separated using column chromatography, eluted with 25% ethyl acetate/ petroleum ether (60-80 °C), to give an unidentified compound (0.2g). The reaction was repeated, sonicating (PS=8) the solution for 2 hours with THF (100 ml) and also using ethylene glycol dimethyl ether (100 ml) as the solvent. These alternatives gave no products.

3.2.3 Photolysis of N-Hydroxypyridine-2-thione

NHPT (1.27g, 10 mmol) and benzene (100 ml) were placed in a three necked round bottomed flask (250 ml) fitted with condenser under nitrogen. With stirring this solution was irradiated with light (500 W bulb) for 3 hours at room temperature. After this time a small amount was removed and analysed by tlc (1:19 ethanol: dichloromethane) which indicated no reaction had occurred. The reaction was then refluxed for a further 6 hours whilst irradiated with light. Again tlc showed little change, therefore benzoyl peroxide (0.3g) and benzene (30 ml) were added and the solution irradiated for a further 3 hours at room temperature. The solvent was evaporated *in vacuo* to yield a solid (1.2g) which was found to be starting material.

3.2.4 Photolysis of N-Hydroxypyridine-2-thione with Separation of Compounds

NHPT (1.27g, 10 mmol) and benzene (100 ml) were placed in a three necked round bottomed flask (250 ml) fitted with condenser under nitrogen. This solution was irradiated with light (500 W bulb) while stirring for 10 hours at room temperature. The benzene was evaporated *in vacuo*, and the resultant solids separated using column chromatography eluted with 10% methanol/dichloromethane.

This produced three main components A (0.35g), B (0.26g), I (0.41g), and several other minor ones (0.05g, total).

3.2.5 Photolysis of N-Hydroxypyridine-2-thione with Toluene as Solvent

The method in reaction 3.2.4 was repeated except the solvent used was toluene (100 ml) for a reaction time of 3 hours. Tlc (1:19 ethanol: dichloromethane) indicated a minute trace of product, which was not isolated.

3.2.6 Photolysis of N-Hydroxypyridine-2-thione with Pivalic Acid

Pivalic acid (10.2g, 0.10 mol), benzene (120 ml), and NHPT (1.27g, 0.01 mol) were charged to a three-necked round bottomed flask (250 ml) under nitrogen and fitted with a condenser. The flask was kept at 35 °C and irradiated with light (500 W bulb) overnight for a total of 17 hours. Tlc indicated only pivalic acid and NHPT present in the reaction mixture.

3.3.1 N-Oxidation of Nicotinamide with Oxone^{R}

Nicotinamide (2.44g, 2 mmol,), wet alumina (10% H_2O, 2.0g) ("Camag" Hopkin & Williams, 100-250 m, neutral, Brockmann activity 1), Oxone^{R} (1.23g, 2.0 mmol) and dichloromethane were added to a round bottomed flask (100 ml specially adapted sonication flask) under nitrogen. The flask was immersed in the sonic cup horn with the cooling water on. The flask was sonicated for 2 hrs, the power setting was adjusted until the maximum agitation was seen within the flask (PS=2). Tlc (1:10 methanol: dichloromethane) indicated that only starting material was present. The flask was removed from the sonic cup horn, and then the sonic probe was immersed directly into the flask, fitted with adaptors to narrow the neck down to provide as close a seal as possible. Extra dichloromethane (75 ml) was added and the mixture was sonicated (PS=7) for a further 1 hour, tlc indicated only starting material present. After a further 1 hour of sonication, tlc indicated the same result. Water was added (15 ml), and the sonication continued for a further 1 hour, after which tlc indicated the formation of a small amount of product. The reaction mixture was discarded.
This experiment was repeated with the sonic probe, and fresh alumina for 90 mins, this produced only a trace of oxide.

3.3.2 N-Oxidation of Nicotinamide with Oxone^{R}

Nicotinamide (24.4g, 20 mmol) was added to a stirred suspension of wet alumina (10% H_2O, 20g) and oxone^{R} (12.3g, 20 mmol) in dichloromethane (250 ml). These were contained in a straight sided round bottomed flange flask (700 ml) fitted with

overhead stirrer and ultrasonic probe under nitrogen. This suspension was sonicated (PS=10) for 2 hours at 15 °C. Tlc (15% ethanol: dichloromethane) indicated no compounds other than starting material present. The temperature was allowed to increase (32-35 °C) whilst sonicating (PS=10) the solution for a further 2 hours. Tlc again indicated only starting material present. Fresh alumina was prepared and added (17% H_2O, 20g) to the suspension and sonicated (PS=10) for a further 2 hours. Tlc indicated only a trace of product. Water (100 ml) was added and the reaction was sonicated (PS=10) for a further 2 hours. At the end of the reaction the resultant emulsion separated, and both phases were sampled. Tlc indicated oxide product and starting material in both phases. The solid was filtered out on a bed of Cellite^R and the solvents evaporated *in vacuo*. The resultant solid was dissolved in hot ethanol (150 ml) and the remaining solid (oxone^R) was filtered out. A portion (approx. 50 ml) of ethanol was evaporated off *in vacuo* and the remaining solution allowed to cool overnight to yield white crystals (20.0g). Tlc indicated these as being approx 50:50 mixture of starting material: oxide.

3.3.3 N-Oxidation of Nicotinamide with Oxone^R

Nicotinamide (24.4g, 20 mmol), wet alumina (10% H_2O, 20g), Oxone^R (12.3g, 20 mmol) and water (250 ml) were charged to a straight sided round bottomed flange flask (700 ml) fitted with ultrasonic probe and overhead stirrer, under nitrogen. The suspension was sonicated (PS=10) for 2 hours. Tlc (15% ethanol: dichloromethane) indicated the reaction to be approx. 50% complete. The reaction was sonicated for a further 2 hours, at which point tlc indicated the reaction had not proceeded further.

3.3.4 N-Oxidation of Nicotinamide with Oxone^R

Nicotinamide (2.44g, 2 mmol), wet alumina (10 %H_2O, 2.0g), Oxone^R (1.23g, 2 mmol) and water (25 ml) were added to a magnetically stirred round bottomed flask under nitrogen. The solution was stirred at room temperature for 72 hours, tlc (15% ethanol: dichloromethane) indicated that the reaction was only partially complete. After a further 72 hours stirring the reaction had obtained reached 50% completion.

3.4.1 Low Temperature Rearrangement of 2,5-Dibromothiophene to 3-Bromothiophene - General method

To a flange flask (250 ml) dried and purged with nitrogen, was charged sodium amide (11.7g) and thiophene (100 ml). This slurry was heated to 55 °C while stirred with an overhead stirrer. A mixture of phase transfer catalyst TDA-1 (0.2g) and

2,5-dibromothiophene (25DBT) (24.2g, 0.1 mol) was added over 15 minutes at 55 °C. The reaction mixture was stirred at 55 °C for 6 hours. Note there is a small exotherm about 30 minutes after the end of the 25DBT addition. The rest of the reaction period required a small amount of heat to maintain the desired temperature. The reaction was worked up by addition of methanol (10g) over 30 mins at 20-25 °C. This was very exothermic and was carried out under a small flow of nitrogen to remove the ammonia. Water (50 ml) was then added at 20-25 °C over 30 minutes to destroy the sodium methoxide. The product was extracted from the reaction mixture by steam distillation, requiring the addition of water (100ml). The product distilled at about 95 °C for the thiophene/water azeotrope, 95-100 °C for the 3-bromothiophene (3BT)/water azeotrope. The fractions after steam distillation were combined in a separating funnel, and the organic phase separated off , which was then analysed using gas chromatography (Method 3.4.5). A typical yield of 3-bromothiophene is 80% with a selectivity ratio of 98:2 for 3BT:2BT.

This general method was used with alterations in the amount of reagents and temperatures. Lower temperatures were obtained by cooling the reaction flask with cardice/ acetone/ water mixture. Sampling was carried out by simply pipetting a sample (10 ml) out of the flask and working it up as per the main reaction except on a smaller scale.
This reaction was repeated under different temperatures, reaction times, sonicated and stirred.

3.4.2 Tribromination of Thiophene with Sodium Bromide/Sodium Bromate

Water (425 ml) was added to a 2 l flange flask, followed by $NaBrO_3$ (150.9g, 1.0 mol), NaBr (205.8g, 2.0 mol), followed by more water (425 ml) and thiophene (67.2g, 0.80 mol). The flask was fitted with a caustic gas scrubber and nitrogen line then stirred and heated to 22 °C. To the reaction mixture was added 30% w/w H_2SO_4 (147.2g conc. H_2SO_4, 343.5 ml water) dropwise over 10 hours (split over 2 days), the reaction was stirred for a further 1 hour, then allowed to settle. The heavy product was separated from the aqueous fraction and washed with dilute NaOH solution (20%, 2 x 50 ml) to yield a brown liquid (2,3,5-tribromothiophene (236g, 92%)) containing 2,5-dibromothiophene (3.8%), 3-bromothiophene (0.02%) and thiophene (0.01%).

3.4.3 Reduction of 2,3,5-Tribromothiophene to 3-Bromothiophene with Zinc/Acetic Acid - General Method.

To a flange flask (500 ml) or the US flask was added zinc dust (58.35g, 0.89 mol), water (138.5 ml), and 2,3,5-tribromothiophene (106.7g, 0.33 mol). This mixture was stirred and heated until the temperature reached 100 °C. Glacial acetic acid (55g, 0.92 mol) was added dropwise over 1 hour then the mixture was refluxed for a further 1 hour. The products were steam distilled out of the flask. The heavier products were separated from the aqueous phase and analysed by GC. Typical yields were 85% 3BT with a selectivity ratio of 99:1 for 3BT:2BT. This reaction was varied by carrying it out at different temperatures with comparisons made between sonicated and stirred reactions.

Table 3.6

		YIELD(%).				
		3BT	3BT/2BT	2,4DBT	3,4DBT	2,3DBT
a)	Std. reaction	85	99:1	2.5	3	-
b)	))), 100°C, PS5	84	95:5	n.a	n.a.	_
c)	75°C	25	>99:1	5	3	0.7
d)	))), 75°C, PS5	40	95:5	4	2.5	-
e)	50°C	11	99:1	5	2	1
f)	))), 50°C, PS5	17	95:5	11	3	0.7
g)	30°C	6	99:1	10	1	2
h)	))), 30°C, PS5	5	99:1	25	7	6

3.4.4 Sonication of 2,3,5-Tribromothiophene/ Zinc/ H_2O

To the US reaction vessel was added zinc dust (8.75g, 0.13 mol), water (10.0 ml) and 2,3,5-tribromothiophene (16.0g, 0.05 mol). The mixture was sonicated (PS=10) until the temperature reached 50 °C. The mixture was maintained at this temperature using the US probe for a further 1 hour. The zinc was filtered out and washed with thiophene (approx. 25 ml) to produce a thiophene solution of product (38.7g). GC indicated 235TBT (46%) and 25DBT (1%) present in the thiophene solution. The starting material which was pale brown at the start of the experiment was decolourised to a clear solution during the experiment.

3.4.5 Gas Chromatography Method used for Analysis of 3-Bromothiophene and 2,3,5-Tribromothiophene Syntheses

A calibration mixture was made up containing thiophene, 2BT, 3BT and 25DBT. The internal standard used was 2,5-dibromo-3-methylthiophene. These were accurately weighed and the corrected weights calculated as shown in the example below;

Table 3.7

Corrected Weight/ g		0.7783	0.2190	0.3488	0.0363	
Sample	Uncorrected Weights/ g	Thiophene	2BT	3BT	25DBT	Others
		Percentage Composition of Components				
Thio	0.7806	99.70	-	-	-	0.30
2-BT	0.2202	0.10	99.37	0.16	0.19	0.27
3-BT	0.3486	-	0.05	99.95	-	-
25-DBT	0.0361	-	0.16	0.04	99.40	0.40
	1.3855					
25DB3MT	0.5379					

A sample of the calibration mixture (0.2 µl) was then injected into the GC under the following conditions:-

Instrument Pye 104, detector back FID, column No 202, column size 25 m x 2 mm, column material fused silica, stationary phase PEG20M, carrier gas nitrogen, inlet pressure 11 psi, splitter flow 70 mls/min, film thickness 0.2 µm, split ratio 70:1, breakthrough time 154 s, linear velocity 16.2 cm/s, make up gas nitrogen, make up flow 26 ml/min, temperature program 150 °C isothermal, injector temp. 210 °C, detector temp. 300 °C, integrator spectra physics, sample size 0.2 µl. The calibration mixture was injected four times to obtain representative data. Using the integration of all four runs, the response factors were calculated as below;

$$RF = \frac{\text{Area of internal standard}}{\text{Weight of internal standard}} \times \frac{\text{Corrected weight of component}}{\text{Area of component}}$$

e.g. Thiophene

$$RF = \frac{77130}{0.5379} \times \frac{0.7783}{279169}$$

$$= 0.3998$$

Table 3.8

Component	Response Factor	Deviation (%)
Thiophene	0.3932	-4.6, +2.4
2BT	0.7749	+1.0, -0.9
3BT	0.7729	+1.0, -0.9
25DBT	1.1872	+1.49, -1.14

These response factors were then used in subsequent runs for calculating actual percentage compositions of mixtures:-

$$\frac{\%\ \text{Internal Standard}}{\text{Area Internal Standard}} \times \text{Area of component} \times \text{RF of component}$$

$$\%\ \text{Internal Standard} = \frac{\text{Weight Internal Standard}}{\text{Weight Sample}} \times 100$$

Table 3.9 Retention Times

Component	R_t min^{-1}
Thiophene	2.56
2BT	3.00
3BT	3.19
25DBT	4.04
24DBT	4.76
23DBT	5.21
34DBT	6.76
235TBT	8.11
2345TBT	20.95
25DB3MT	4.76

3.4.6 Sonication of 2,5-Dibromo-3-methylthiophene with Zinc/ Acetic Acid

To a straight sided round bottomed flask (700 ml) fitted with sonic probe and overhead stirrer was added 25-DB3MT (84.5g, 0.33 mol), water (390 ml) and zinc dust (29.0g, 0.44 mol). Glacial acetic acid (27.5g, 0.46 mol) was added dropwise over 15 minutes while the solution was stirred and sonicated (PS=10). The reaction was continued for a further 75 minutes while maintaining the solution at 25-30 °C with a cardice/acetone/water slurry. The zinc was then filtered out and washed with thiophene. GC analysis indicated thiophene, starting material and 2-bromo-3-methylthiophene present with a trace of 2-bromo-4-methylthiophene. The ratio of 25B3MT: 2B3MT was approximately 4:1.

3.5.1 Attempted Coupling of 2-Bromothiophene - General Method

2BT (48.9g, 0.30 mol) and THF (100 ml) (dried over CaH_2) were charged to the US flask under nitrogen. This mixture was sonicated (PS=5) or stirred while lithium powder (2.28g, 0.33 mol) was added cautiously over 20 minutes. The reaction was maintained at 35 °C using an ice/salt/water bath. Once the lithium addition was complete the power setting on the probe was increased (PS=9), and the reaction continued for a further 100 minutes. The reaction was then quenched with methanol

(15 ml) very cautiously (care was taken because this reaction is violent and exothermic, there can also be an induction period), then water (50 ml). A further addition of water was made (100 ml) and the organics were extracted with diethyl ether (3 x 50 ml), washed with brine (3 x 100 ml) and dried ($MgSO_4$). If the solvent was removed it was distilled off, not removed *in vacuo*, because the monobromothiophenes tended to azeotrope off with the ether. Most reaction mixtures were analysed by simply taking a sample of the etheral solution and analysing it using GC-MS (method 3.5.2) which gave a percentage yield of each component **relative to each other**, yields quoted are not absolute. The products were also steam distilled out of the reaction mixture by simply refluxing the aqueous mixture and collecting the azeotrope, upon which the heavier organics separate out and can be isolated. This affords a purer product than solvent extraction, which contains residues such as pitch, a common problem with thiophene reactions.
This experiment was used with alternative temperatures, times, and reagent form, e.g. lithium granules instead of powder (Table 3.10).

Key for table 3.10

PS = power setting on ultrasonic probe, (l) = lumps, (g) = granular, (p) = powder, (w) = wire, SCH = sonic cup horn, BrITh = bromoiodothiophene, nBuCl = n-butyl chloride, Th = thiophene, THF = Tetrahydrofuran, DMF = dimethylformamide, Cu = copper flitters.

Table 3.10

Attempted Coupling Reactions of 2-Bromothiophene

No.	Conditions	Thio	2BT	3BT	25DBT	24DBT	23DBT	34DBT	TBT
a)	Li (l), PS8		100						
b)	Li (g), PS8	41	51	3		2.5	3.5		
c)	Li (g), SCH PS8	25	7	20	0.5	7	5.5	15	19.5
d)	Li (p), PS9	8	45	25	1	1	1	17	1
e)	Li (p), stir	20	70	3.5	2	3	0.5	0.5	
f)	Li (p), PS9 5^0C	34	13	14	3.5	21	9	2	3.5
g)	Li (p), PS9 -50^0C	47	7.5	15		10	7.5	7.5	5
h)	Li (g), PS9 -50^0C	58	36.5	2	1.5	1			
i)	Li (p), 5^0C stir	39	60	1					
j)	Li (p), -50^0C stir	39	59	1					
k)	Li (p), reflux stir	28	39	19	2	2	1	9	
l)	As (d) iodophene quench	21	70	2	1.5	0.5	5 BrITh		
m)	Th, PS3, Li (p), nBuCl, 25^0C		100						
n)	As (d) with anthracene	26	7	42	9	6	6	3	

Table 3.10 continued

No.	Conditions	Thio	2BT	3BT	25DBT	24DBT	23DBT	34DBT	TBT
o)	As (n) - stirred		88	3	3.5	0.5	0.5	3	0.5
p)	As (n) - 5hrs	32	32	25	0.5	1	1	8.5	
q)	As (n) - stirred, reflux	8	57	23	1	0.5	0.5	8	1
r)	Th, PS9, Li (p)		100						
s)	As (r), stirred, reflux		100						
t)	THF/ Th, Li (p), PS10, 105min		100						
u)	As (t), 50^0C		100						
v)	As (t), stirred, reflux	40	58	1.5					
w)	DMF, Cu, PS9		100						
x)	DMF, Cu, PS9 Phenol		100						
y)	Na (w), PS5, 30min, 25^0C	47	16	10	1	5.5	4.5	5	10
z)	As (y), stir, reflux	20	70	5	1	1		1.5	
a1)	As (y), stir		100						

3.5.2 Gas Chromatography - Mass Spectrometry (GC-MS) Method Used for Analysis of Above Reaction Mixtures

A calibration mixture was made up containing 0.10g each of thiophene, 2BT, 3BT, 25DBT, 34DBT, 235TBT, made up to 10.0 ml with diethyl ether. A sample (1.0 µl) of this solution was then analysed using a GC-MS under the following conditions:- GC Hewlett Packard 5890 series II, detector Hewlett Packard 5971A mass selective detector, integrator Hewlett Packard Chemstation, carrier gas helium, inlet pressure 5psi, splitter flow 12.50 ml min^{-1}, split ratio 25:1, column flow 0.5 ml min^{-1}, solvent delay 2.50 min, linear velocity 20 cm s^{-1}, film thickness 0.33 µm, stationary phase DB5MS polymethylsiloxane 5% methyl substituted with phenyl, column material silica glass capillary, column size 25 m x 0.2 mm. Temperature program; initial temp = 100 °C, initial time = 3.00 min, ramp = 20°C min^{-1}, Final temp = 210 °C, final time = 3.50 min, total time = 12.00 min, sample size 1.0 µl, injector temp = 250 °C, detector temp = 280 °C.

A sample was analysed using the GC-MS several times to obtain a representative result. The response factors from the integration values of each compound were then calculated as follows:-

Table 3.11

Component	Response Factor
Thiophene	1.00
Monobromothiophenes	0.50
Dibromothiophenes	0.33
Tribromothiophene	0.25

To obtain a relative concentration of a component within a reaction mixture the following calculation was applied:-

Area of component = Integration of Component x Response Factor of Component

% of Component = Area of Component / Total Area of Components

Table 3.12 Retention times

Component	R_t min^{-1}
Thiophene	2.59
2BT	4.73
3BT	5.03
25DBT	7.57
24DBT	7.86
23DBT	7.99
34DBT	8.45
234TBT	10.20
235TBT	11.02

3.5.3 Attempted Coupling of 2-Bromothiophene - with Anthracene

Identical to the general method except anthracene (2.67g, 0.015 mol) was added with the initial reaction mixture. At the end of the reaction the mixture was very viscous, therefore the products were steam distilled out of solution. A sample (0.1g) of the products was diluted in diethyl ether and analysed using GC-MS.

3.5.4 Attempted Coupling of 2-Bromothiophene -Cup Horn Sonication

2-Bromothiophene (12.2g. 0.075 mol) and THF (25 ml) were added to a round bottomed flask (50 ml) (with side neck for nitrogen inlet) which was immersed into the sonic cup horn with water cooling on. Lithium powder (0.57g, 0.08 mol) was added over 2 minutes while the flask was sonicated (PS=5) for a total of 2 hours. The work up was as the general method (Reaction 3.5.1), scaled down accordingly.

3.5.5 Attempted Coupling of 2-Bromothiophene -Thiophene used as Co-Solvent

2-Bromothiophene (24.45g, 0.15 mol), thiophene (50g, 0.595 mol) and THF (150 ml) were charged to the US flask under nitrogen. This reaction mixture was sonicated (PS=5) at 35 °C, during which time powdered lithium (1.14g, 0.165 mol) was added over 15 minutes. The reaction mixture was then sonicated for a further 105 minutes. The work up was as the general method. GC-MS indicated only starting material present.

3.5.6 Attempted Coupling of 2-Bromothiophene - Butyl Chloride Lithiation

Thiophene (840 mg, 10 mmol), n-butylchloride (930 mg, 10 mmol), THF (20 ml) and lithium granules (140 mg, 20 mmol) were placed into a two necked round bottomed flask (100 ml). This mixture was sonicated using the cup horn (PS=2) set to provide maximum agitation within the mixture. During the reaction additional THF (10 ml) was added. At the end of the sonication the flask was removed from the sonic cup horn and stirred magnetically while 2-bromothiophene (1.63g, 10 mmol) was added dropwise over 5 minutes, then stirred for a further five minutes. The reaction was then cautiously quenched with methanol (10 ml), followed by water (20 ml). The organics were extracted with diethyl ether (3 x 15 ml), washed with brine (3 x 15 ml), and dried ($MgSO_4$). The solution was analysed by GC-MS which indicated only thiophene and 2-bromothiophene present.

3.5.7 Attempted Coupling of 2-Bromothiophene - Using Sodium

2-Bromothiophene (10g, 0.061 mol) was dissolved in THF (50 ml) within the US flask under nitrogen. To this was added sodium wire (1.54g, 0.067 mol) over 5 minutes, while the reaction mixture was stirred or sonicated for a total of 30 min. Work up was as the general method and scaled down appropriately.

3.5.8 Attempted Ullman Coupling of 2-Bromothiophene

2-Bromothiophene (5.0g, 0.03 mol) was placed in the US flask with copper flitters (9.52g, 0.15 mol) and DMF (75 ml). This was sonicated (PS=10) for 2 hours under nitrogen. After filtering the solution GC-MS indicated only starting material present.

3.5.9 Attempted Phenoxylation of 2-Bromothiophene

2-Bromothiophene (5.0g, 0.03 mol), phenol (2.8g, 0.03 mol), copper flitters (9.52g, 0.15 mol) and DMF (75 ml) were sonicated (PS=10) in the US flask for 2 hours under nitrogen. GC-MS indicated only starting material present.

3.5.10 Coupling of Bromobenzene

Bromobenzene (47.11g, 0.30 mol), and THF (100 ml) were added to the US flask under nitrogen. The reaction was sonicated (PS=3) while lithium powder (2.28g, 0.33 mol) was cautiously added over 40 minutes. The power was increased (PS=5) and the reaction was sonicated for a further 80 minutes. The reaction temperature was maintained (25-30 °C) using an ice/salt/water bath. The reaction was quenched with ethanol (10 ml) added slowly over 10 minutes, then water (10 ml) was added with

stirring over 10 minutes. This produced a small amount of heat and frothing. The mixture was transferred to a separating funnel, water (100 ml) added, and the organics extracted with ether (3 x 50 ml), washed with brine (3 x 100 ml), dried ($MgSO_4$), and the solvent removed *in vacuo* (17.7g). GC-MS indicated the crude product to be approximately 50% biphenyl.

3.5.11 Attempted Coupling of 3-Bromothiophene - Lithium Granules and Sonic Cup Horn

3-Bromothiophene (4.89g, 0.03 mol), and THF were added to a side necked 50 ml round bottomed flask under nitrogen. This was immersed in the sonic cup horn and sonicated (PS=1) while the lithium granules (0.23g, 0.033 mol) were added over 5 minutes. The reaction mixture was sonicated for a further 115 mins. at 25 °C. Work up was as previous solvent extraction methods (reaction 3.5.1), to scale. GC-MS indicated starting material (81%), 2-bromothiophene (2%) and thiophene (17%) present.

3.5.12 Attempted Coupling of 3-Bromothiophene - Lithium Powder and Sonic Probe

3-Bromothiophene (10g, 0.061 mol) was dissolved in THF (50 ml) in the US flask under nitrogen. The reaction mixture was sonicated (PS=5) while the lithium powder (0.47g, 0.067 mol) was added over 5 minutes. The reaction was sonicated for a further 115mins. Work up and GC-MS as before (reaction 3.5.1) indicated starting material (82%), 2-bromothiophene (1%), and thiophene (17%) present.

3.5.13 Attempted Coupling of 3-Bromothiophene - Sodium Wire and Sonic Probe

3-Bromothiophene (5g, 0.031 mol) in dry THF (50 ml) was sonicated (PS=5) with the sonic probe in the US flask under nitrogen. to this was added sodium wire (0.77g, 0.34 mol) over 2 minutes, after 40 minutes the power was increased (PS=8) and sonicated for a further 80 minutes. After work up as before (reaction 3.5.1) GC-MS indicated thiophene (26%), 2-bromothiophene (1%) and 3-bromothiophene (73%) present.

3.5.14 Attempted Coupling of 2-Chlorothiophene - Lithium Powder and Sonic Cup Horn

2-Chlorothiophene (3.56g, 0.03 mol) in dry THF (10 ml) was placed in a 50 ml conical flask under nitrogen. This was sonicated in the sonic cup horn (PS=5) and lithium granules (0.23g, 0.033 mol) added over 10 minutes. The mixture was

sonicated for a total of 2 hours. The reaction was quenched with methanol (1.5 ml) and H_2O (5 ml). Work up (as reaction 3.5.1) followed by GC-MS indicated only starting material.

3.5.15 Attempted Ullman Coupling of 2-Chlorothiophene

2-Chlorothiophene (1.0g, 0.008 mol), copper flitters (2.68g, 0.04 mol), in DMF (20 ml) were placed in a conical flask (50 ml) under nitrogen and sonicated in the sonic cup horn (PS=5) for 2 hours. Work up followed by GC-MS indicated only starting material and a small trace of 2,5-dichlorothiophene.

3.5.16 Attempted Coupling of 2,5-Dibromothiophene - Lithium Powder and Sonic Cup Horn

2,5-Dibromothiophene (7.26g, 0.03 mol) and THF (10 ml) were placed within a side necked round bottomed flask (50 ml) under nitrogen, and immersed in the sonic cup horn. The reaction mixture was sonicated (PS=1) and lithium (0.23g, 0.33 mol) added over 10 minutes, the power was increased (PS=5) for a further 110 minutes. After work up and GC-MS as above (reaction 3.5.0) the following products were observed, thiophene (1.5%), 2BT (28%), 3BT (2.5%), 25DBT (26%), 24DBT (1.5%), 23DBT (1.5%), 34DBT (16%), 235TBT (23%).

3.6.1 Methoxylation of 2-Bromothiophene With Copper Metal

a) 2-Bromothiophene (10.0g, 0.06 mol), 30% sodium methoxide solution in methanol (55g, 0.30 mol), and copper wire (4.0g, 0.063 mol, 10 mm pieces) were charged to the US flask under nitrogen. The reaction mixture was sonicated (PS=6) for 2 hours at 55 °C. The reaction was quenched with water (10 ml), then more water was added and the products were steam distilled out of the flask. The heavier organics were removed using a separating funnel. A sample (0.1g) of the organic fraction was dissolved in diethyl ether (10 ml) and this solution was analysed by GC-MS using method 3.5.2 outlined for the analysis of bromothiophenes. The analysis was a simple comparison, and did not take any response factors into account. GC-MS indicated only a very small trace of methoxythiophene (MeOTh) present.

b) Reaction (a) was repeated with stirring only and refluxed for 25 hours, which produced thiophene (10%), MeOTh (4%), the remainder was starting material.

c) Reaction (b) was repeated with the power setting increased (PS=8) at 30 °C for 2 hours, with less 30% $NaOCH_3$ solution (27.5g, 0.15 mol), extra methanol (30 ml), again only produced a trace of MeOTh.

d) Reaction (c) was repeated using copper flitters insead of copper wire. Sonicating the solution (PS=8) for 2 hours at 30 °C afforded starting material and MeOTh (2%).
e) Reaction (d) was repeated with reduced power (PS=5), extra methanol (30 ml) and potassium iodide (0.06g, 0.2 mmol). These conditions afforded MeOTh (9.5%).

f) Repeating (d) and replacing the solvent with DMF (30 ml) afforded MeOTh (trace) and 2,5-dibromothiophene (30%).

3.6.2 Methoxylation of 2-Bromothiophene - With Copper Oxide

a) 2-Bromothiophene (10.0g, 0.06 mol), 30% methanolic $NaOCH_3$ solution (27.5g, 0.15 mol), methanol (30 ml), CuO (1.22g, 0.015 mol), were charged to the US flask and sonicated (PS=8) for 2 hours. The reaction mixture was maintained at 30 °C with an ice/salt/water bath. The reaction was quenched with water (10 ml), more water was added and the products were steam distilled and analysed using GC-MS as the previous methoxylation. GC-MS indicated MeOTh was produced in a small yield (3%).

b) This reaction was repeated with KI (0.06g, 0.2 mmol), which afforded MeOTh (24%, repeat 18%).
Variations of the reaction with KI were carried out.

c) Stirred only (6% MeOTh).

d) Temperature at 50 °C (7.5% MeOTh).

e) Power setting 5 at 15 °C (3% MeOTh).

f) Sonic cup horn (SM only).

3.6.3 Methoxylation of 2-Bromothiophene - With Copper Acetyl Acetonate and Copper Oxide

a) 2-Bromothiophene (10.4g, 0.062 mol), 30% methanolic $NaOCH_3$ solution (35 ml), KI (0.08g, 0.5 mmol), copper(II)acetyl acetonate (0.159g, 6.1×10^{-4} mol), CuO (1.59g, 0.020 mol), TDA-1 (0.08g), and methanol (20 ml) were charged to the US flask under nitrogen. This solution was sonicated (PS=8) for 2 hours, while the

solution was maintained at 30 °C using an ice/salt/water bath. Steam distillation of the products followed by GC-MS indicated a low yield of MeOTh (11.2%).

b) Using the same reagents as above and heating them to reflux for 14 hours without ultrasound produced MeOTh (40%).

3.7.1 Silylation of 2-Bromothiophene - Sonication

The Suslick cell was purged with nitrogen and to this was added 2-Bromothiophene (0.82g, 5 mmol), THF (4 ml), chlorotrimethylsilane (TMSCl) (0.54g, 5 mmol), and magnesium (0.12g, 5 mmol). The Suslick cell was then sonicated (PS=2) for 40 minutes in the sonic cup horn. The reaction mixture was quenched with water (10 ml) and the resultant solution filtered. At this point a portion of the heavier organics were removed in a separating funnel. The aqueous phase was then extracted with diethyl ether (2 x 10 ml) and discarded. The organic phases were combined, washed with water (2 x 10 ml), dried ($MgSO_4$) and the solvent removed by distillation, not *in vacuo* where the product is easily evaporated out of the flask, to yield the green liquid product (0.57g, 73%).

A kinetic study of this reaction, which involved taking a sample (0.1 ml) of the reaction mixture every 5 minutes, and using GC-MS analysis, indicated the reaction was complete after 15 minutes.

Analysis note: Analysis by GC-MS was carried out for all silylation work using the same method (3.5.2) as used for the bromothiophenes, a simple comparison between components was made and no response factors were utilised.

3.7.2 Silylation of 2-Bromothiophene - Reflux

a) Reagents, work-up, and analysis were identical to the sonicated reaction (3.7.1) except the reaction was added to a 25 ml round bottomed flask fitted with condenser and purged with nitrogen. The reaction mixture was then refluxed for 2 hours. GC-MS indicated thiophene (18%), 2BT (16%), and 2-(trimethylsilyl)thiophene (2-TMSTh) (66%) present. There was also a significant amount of hexamethylsiloxane, suggesting the reaction had not gone to completion.

b) Reaction (a) was repeated on twice the scale, 2-BT (1.64g, 10 mmol), THF (8 ml), TMSCl (1.08g, 10 mmol) and magnesium (0.24g, 10 mmol) were placed in a three-necked round bottomed flask (100 ml) purged with nitrogen. The mixture was refluxed with stirring, sampling (0.1 ml) approximately every hour. The following concentrations were observed: 1.5 hrs , thiophene (13%), 2BT (21%), 2-TMSTh

(66%); 2.5 hrs, thiophene (15%), 2BT (21%), 2-TMSTh (64%); 3.5 hrs, thiophene (16%), 2BT (22%), 2-TMSTh (62%); At 3.5 hrs extra TMSCl (0.54g, 5 mmol was added; 4 hrs, thiophene (28%), 2BT (22%), 2-TMSTh (50%); At 4 hrs extra magnesium (0.12g, 5 mmol) was added; 5 hrs, reaction stopped, thiophene (47%), 2BT (5%), 2-TMSTh (48%).

c) Reaction (a) was repeated except it was stirred at room temperature with no sonication. The following concentrations were observed: 75 min., 2BT (61%), 2-TMSTh (39%); 4 hrs, 2BT (26%), 2-TMSTh (74%); 7hrs, 2BT (26%), 2-TMSTh (74%).

d) Reaction (c) was repeated with extra TMSCl (0.675g total, 6.25 mmol). The following concentrations were observed; 4 hrs, 2BT (54%), 2-TMSTh (46%); 24 hrs, 2BT (5%), 2-TMSTh (95%), bithiophene (trace); 32 hrs, 2-TMSTh (96%), bithiophene (4%).

3.7.3 Attempted Silylation of 3-Bromothiophene

a) 3-Bromothiophene (0.82g, 5 mmol), THF (4 ml), chlorotrimethylsilane (0.54g, 5 mmol) and magnesium (0.12g, 5 mmol) were placed in a nitrogen purged Suslick cell, then sonicated (PS=2) in the sonic cup horn for 5 hrs, with the cooling water on. Work up and analysis of a sample from the reaction mixture (the method of which was identical to reaction 3.7.1) showed only starting material present. The reaction mixture was then sonicated in a Kerry ultrasonic cleaning bath for 8 hrs. Analysis by GC-MS again showed only starting material present.

b) The above reaction was repeated with sonication using the sonic probe (PS=3) immersed in the reaction mixture for 3 hrs, with the flask cooled with ice/water. GC-MS indicated only starting material present.

3.7.4 Attempted Silylation of 3-Bromothiophene.

3-Bromothiophene (3.28g, 20 mmol), THF (16 ml), chlorotrimethylsilane (2.16g, 20 mmol) and magnesium (0.48g, 20 mmol) were placed in a wide necked, side armed round bottomed flask (50 ml US flask) purged with nitrogen and cooled in an ice bath. The flask was sonicated (PS=2) for 10 minutes then the power was increased (PS=8) for a further 110 minutes. Work up and GC-MS indicated starting material only present.

3.7.5 Silylation of 2,3,5-Tribromothiophene

2,3,5-Tribromothiophene (0.53g, 0.167 mmol), magnesium (0.12g, 5 mmol), THF (4 ml) and chlorotrimethylsilane (0.54g, 5 mmol) were added to the Suslick cell under nitrogen. This was immersed in the sonic cup horn and irradiated for 4 hours (PS=2) with a sample (0.1 ml) taken after 2 and 3 hours. Work up and analysis as per silylation of 2-bromothiophene (Reaction 3.7.1).

This reaction was repeated with no ultrasound under reflux for 4 hours. Table 3.13 below illustrates the reaction mixture obtained after the respective time periods.

Table 3.13

Compound	2hrs	3hrs	4hrs
DBTh	1	1	1
DBTh	5	5.5	5.5
BrSiTh	3	3	3
BrSiTh	2	2	2
TBT	8	8	8
DBrSiTh	24	25	25
DBrSiTh	53	55	55
Unknown (M/Z 364)	4	1	-

BrSiTh = bromo-(trimethylsilyl)thiophene

DBTh = dibromothiophene

DBrSiTh = dibromo-(trimethylsilyl)thiophene

3.7.6 Silylation of 2,3,5-Tribromothiophene - Concentrated Solution

2,3,5-Tribromothiophene (1.06g, 3.33 mmol), magnesium (0.24g, 10 mmol), chlorotrimethylsilane (1.08g, 10 mmol), and THF (4 ml) were added to the Suslick cell under nitrogen, immersed in the sonic cup horn and sonicated (PS=2) for 2 hours. Work up and analysis as per Reaction 3.7.1. GC-MS indicated dibromothiophene (1.5%), two isomers of bromo-(trimethylsilyl)thiophene (5.5%, 3.5%), and two isomers of dibromo-(trimethylsilyl)thiophene (13%, 77%). The above reaction was repeated except it was refluxed for 2 hours. GC-MS indicated dibromothiophene (1.5%), two isomers of bromo-(trimethylsilyl)thiophene (5.5%, 3.5%), and two isomers of dibromo-(trimethylsilyl)thiophene (13%, 77%).

3.7.7 Silylation of Tetrabromothiophene

Tetrabromothiophene (1.0g, 2.5 mmol), chlorotrimethylsilane (1.08g, 10 mmol), magnesium (0.24g, 10 mmol) and THF (4 ml) were added to the Suslick cell under nitrogen and sonicated (PS=2) in the sonic cup horn for 2 hours. Work up and analysis as per silylation of 2-bromothiophene (Reaction 3.7.1). GC-MS indicated the products as tribromo-(trimethylsilyl)thiophene (59%), dibromo-bis-(trimethylsilyl)thiophene (25%), dibromo-(trimethylsilyl)thiophene (12%), tribromothiophene (4%), and dibromothiophene (1%).

This reaction was repeated with no ultrasound under reflux for 2 hours. GC-MS indicated a similar product mixture tribromo-(trimethylsilyl)thiophene (42%) dibromo-(trimethylsilyl)thiophene (25%) dibromo-bis-(trimethylsilyl)thiophene (26%), tribromothiophene (5.5%), and 2,5-dibromothiophene (2.5%).

3.7.8 Silylation of 2-Bromo-3-methylthiophene

a) 2-Bromo-3-methylthiophene (0.88g, 5 mmol), magnesium (0.12g, 5 mmol), THF (4 ml) and chlorotrimethylsilane (0.54g, 5 mmol) were added to the Suslick cell under nitrogen. This was immersed in the sonic cup horn and sonicated (PS=2) for 1 hour. Work up and analysis as per silylation of 2-bromothiophene (reaction 3.7.1.).

b) The above reaction was repeated on twice the scale. 2-Bromo-3-methylthiophene (1.93g, 11 mmol), THF (8 ml), chlorotrimethylsilane (1.08g, 10 mmol), magnesium (0.24g, 10 mmol) were added to the Suslick cell which was immersed in the sonic cup horn and sonicated (PS=2) for 1 hour. Work up as above was carried out to leave a crude liquid product mixture. In an attempt to separate the crude mixture it was subjected to simple vacuum distillation. The vacuum source was a water pump. The distillation was unsuccessful for two reasons. A) The distillate condensed in the condenser and was too viscous to run into the receptor, B) the distillate contained mixed fractions.

3.7.9 Silylation of 2-Bromo-3-methylthiophene - 2 Equivalents of Magnesium

2-Bromo-3-methylthiophene (3.54g, 20 mmol), THF (16 ml), chlorotrimethylsilane (2.16g, 20 mmol), and magnesium (0.48g, 20 mmol) were charged to the Suslick cell under nitrogen. Using the sonic cup horn the reaction mixture was sonicated (PS=2) for 1 hour. The reaction was quenched with water (40 ml), filtered, extracted with ether (3 x 20 ml), washed with water (3 x 20 ml), dried ($MgSO_4$), and the solvent removed by distillation to give a crude reaction mixture (2.2g). The product mix was

subjected to bulb to bulb distillation. The silylated product distilled at 100 °C at 375 mm Hg, this gave an ambient boiling point of approx 130 °C. Bulb to bulb distillation provided relatively pure product (540 mg, 95%) for analysis.

3.7.10 Silylation of 2-Bromo-3-methylthiophene - 1.5 Equivalents of Magnesium

a) 2-Bromo-3-methylthiophene (0.88g, 5 mmol), magnesium (0.18g, 7.5 mmol), chlorotrimethylsilane (0.60g, 5.5 mmol), and THF (4 ml) were charged to the Suslick cell under nitrogen. The cell was sonicated (PS=2) using the sonic cup horn for 1 hour. The reaction mixture was worked up and analysed with GC-MS as per silylation of 2-bromothiophene (reaction 3.7.1), which indicated the presence of 2-(trimethylsilyl)-3-methylthiophene (67%, 57% yield), and 3-methylthiophene (33%) in the crude reaction product (0.75g).

b) The above reaction was repeated without ultrasound under reflux for 2 hours. GC-MS indicated 2-(trimethylsilyl)-3-methylthiophene (85%), and 3-methylthiophene (15%) present in the crude reaction mixture (0.75g).

3.7.11 Silylation of 2,5-Dibromothiophene - Ultrasound

a) 2,5-Dibromothiophene (0.60g, 2.5mmol), chlorotrimethylsilane (0.54g, 5mmol), magnesium (0.12g, 5mmol) and THF (4ml) were added to the Suslick cell under nitrogen. This was sonicated in the sonic cup horn (PS=2) for 40 minutes. Work up and analysis was as per silylation of 2-bromothiophene (reaction 3.7.1). GC-MS indicated a 50:50 mixture of 2-(trimethylsilyl)thiophene and bis-2,5-(trimethylsilyl)thiophene.

b) Reaction (a) was repeated for 2 hours. GC-MS indicated 2-(trimethylsilyl)thiophene (17%), bis-2,5-(trimethylsilyl)thiophene (58%), 2-bromo-5-(trimethylsilyl)thiophene (2%), 2-bromothiophene (4%).

c) Reaction (a) was repeated using less solvent (2 ml THF) over a reaction time of 15 min. GC-MS indicated (trimethylsilyl)thiophene (11%), 2,5-dibromothiophene (7%), bis-2,5-(trimethylsilyl)thiophene (70%), 2-bromo-5-(trimethylsilyl)thiophene (4%).

d) Reaction (a) was repeated with twice the amount of magnesium (0.24g, 10 mmol) over 1 hour duration. GC-MS indicated 2-(trimethylsilyl)thiophene (28%), and bis-2,5-(trimethylsilyl)thiophene (72%).

e) Reaction (a) was repeated with twice the amount of chlorotrimethylsilane (1.08g, 10 mmol) over 20mins duration. GC-MS indicated 2-(trimethylsilyl)thiophene (13%), 2,5-dibromothiophene (18%), bis-2,5-(trimethylsilyl)thiophene (64%), 2-bromo-5-(trimethylsilyl)thiophene (5%).

f) Double scale reflux equivalent of reaction (a) over 5 hours, with sampling (0.1 ml) every hour. GC-MS indicated thiophene (38%), 2-(trimethylsilyl)thiophene (17%), 2,5-dibromothiophene (11%), bis-2,5-(trimethylsilyl)thiophene (34%).

3.7.12 Silylation of 2,5-Dibromothiophene - 2 Equivalents of Reagents - Varied Solvent Levels

a) 2,5-Dibromothiophene (0.60g, 2.5 mmol), chlorotrimethylsilane (1.08g, 10 mmol), magnesium (0.24g, 10 mmol), and THF (4 ml) were added to the Suslick cell under nitrogen. The cell was sonicated (PS=2) in the sonic cup horn for 2 hours. GC-MS indicated 2-(trimethylsilyl)thiophene (17%), and bis-2,5-(trimethylsilyl)thiophene (67%).

b) Reaction (a) was repeated with reduced quantities of THF (2ml). After 5 minutes the solution was a thick slurry, after 15 minutes it started to turn brown and was therefore quenched, worked up, and analysed as before. GC-MS indicated 2-(trimethylsilyl)thiophene (18%), 2,5-dibromothiophene (7%), bis-2,5-(trimethylsilyl)thiophene (70%), 2-bromo-5-(trimethylsilyl)thiophene (4%).

c) Reaction (a) was repeated with additional THF (6 ml total) over 20 minutes. GC-MS indicated 2-(trimethylsilyl)thiophene (17%), and bis-2,5-(trimethylsilyl)thiophene (83%).

d) Reaction (a) was repeated with additional THF (10 ml total) over 90 minutes to produce a complex reaction mixture, the reaction mixture was sampled after 20 minutes, and 1 hour. GC-MS indicated after 20 minutes 2-(trimethylsilyl)thiophene (9%), 2-bromothiophene (4%), bis-2,5-(trimethylsilyl)thiophene (23%), 2-bromo-5-(trimethylsilyl)thiophene (55%), 2,5-dibromothiophene (9%); after 1hr 2-bromothiophene (5%), 2-(trimethylsilyl)thiophene (9%), 2,5-dibromothiophene (2%), 2-bromo-5-(trimethylsilyl)thiophene (61%), bis-2,5-(trimethylsilyl)thiophene (23%); after 90 minutes 2-bromothiophene (5%), 2-(trimethylsilyl)thiophene (9%), 2,5-dibromothiophene (2%), 2-bromo-5-(trimethylsilyl)thiophene (61%), bis-2,5-(trimethylsilyl)thiophene (23%).

e) Reaction (d) was repeated with the reagents at half scale with the solvent level remaining the same, effectively halving the concentration: 2,5-Dibromothiophene (0.30g, 1.25 mmol), chlorotrimethylsilane (0.54g, 5 mmol), magnesium (0.12g, 5 mmol), and THF (10 ml) were added to the Suslick cell under nitrogen and sonicated (PS=2) over 2 hours. GC-MS indicated 2-(trimethylsilyl)thiophene (1.5%), 2,5-dibromothiophene (55%), bis-2,5-(trimethylsilyl)thiophene (2.5%), 2-bromo-5-(trimethylsilyl)thiophene (35%), 2-bromothiophene (6%).

f) Reaction (e) was repeated over 7 hours, with a sample (0.1 ml) taken after 4 hours. GC-MS indicated after 4 hours 2-bromothiophene (11%), 2,5-dibromothiophene (17%), 2-bromo-5-(trimethylsilyl)thiophene (71%); after 7hours 2-bromothiophene (13%), 2,5-dibromothiophene (9%), 2-bromo-5-(trimethylsilyl)thiophene (77%).

Table 3.14

		Yields					
	Conditions	Th	SiTh	DBTh	DSiTh	BrSiTh	2BT
a)	)))), 2hrs, r.t		17		58	2	4
b)	)))), 2hrs, 2 eq		33		67		
c)	)))), 1hr, 2 eq Mg only		28		72		
d)	)))), 20min, 2 eq TMSCl only		13	18	64	5	
e)	Reflux, 5hrs	38	17	11	34		
f)	)))), 15min, 1eq, 0.5 THF		11	7	75	6	1
g)	)))), 15min, 2eq, 0.5 THF		18	7	70	4	
h)	)))), 20min, 2eq, 1.5 THF		17		83		
i)	)))), 90min, 2eq, 2.5 THF		9	2	23	61	5
j)	)))), 2hrs, 4eq, 5 THF		1.5	55	2.5	35	6
k)	)))), 7hrs, 4eq, 5 THF			9		77	13

Th = Thiophene, SiTh = (trimethylsilyl)thiophene, DBTh = dibromothiophene
DSiTh = bis-(trimethylsilyl)thiophene, BrSiTh = bromo(trimethylsilyl)thiophene
eq = No equivalents of reagent per bromine atom

3.8.0 Calorimetry

All calorimetry was carried out in a Mettler RC1 calorimeter fitted with a 2 l vessel, with no lid fitted. Settings; F/C open 0.6, water flow n.a, virtual volume 1.33-1.35, stirrer 600 rpm, chiller -20 °C. Calibration; Hold at 20 °C for 10 minutes, calibrate at 20 °C for 10 minutes, hold at 20 °C for 20 minutes. The ultrasonic probe was inserted to a depth of 7.1 cm from the tip in all cases unless otherwise stated.

3.8.1 Calorimetry - Effect of Power Setting/Tuning/Pulse/Temperature

Water (1250 ml) was charged to the vessel. After calibration at 20 °C, the probe was turned on for 30 minutes at power setting 1.0. After a short stabilising period (10 minutes) the procedure was repeated at power settings up to 10.0 in steps of 1.0 for 10 minutes. The reactor was heated to 30 °C and the probe turned on for 10 minutes at setting 5.0. The temperature was reduced to 20 °C and the probe "detuned" to 50% for 10 minutes. A further check at power setting 5.0 for 10 minutes was made before adding water (250 ml) after which the probe was turned on for 10 minutes at power setting 5.0. The reactor was then calibrated again at 20 °C.

Table 3.15 Power Absorbed

Probe setting	Time(mins.)	Integral(kJ)	Average(W)
1.0	30	12.8	7.1
2.0	10	8.5	14.2
3.0	10	13.5	22.4
4.0	10	18.7	31.1
5.0	10	24.4	40.7
6.0	10	30.3	50.5
7.0	10	36.7	61.2
8.0	10	43.4	72.4
9.0	10	52.4	87.3
10.0	10	59.8	99.6
5.0[1]	10	23.6	39.3
5.0[2]	10	22.6	37.6
5.0[3]	10	12.2	20.4
5.0[4]	10	23.6	39.3
5.0[5]	10	26.0	43.3

NOTES: 1 - at 30 °C; 2 - detuned to 50%; 3 - pulsed at 50%; 4 - re-check at 20 °C; 5 - after water addition.

3.8.2 Calorimetry - Effect of Solvent (Vapour Pressure)

The solvent to be studied (1250 ml) was charged to vessel. After calibration at 20 °C, the probe was turned on for 10 minutes at power setting 5.0.

Table 3.16

Heat output

Solvent	Integral(kJ)	Average(W)
Toluene	21.5	35.8
Acetone	18.5	30.8
Butan-1-ol	22.5	37.5
Water	24.4	40.7
Methanol	19.4	32.3
THF	20.8	34.7
Thiophene	23.4	39.0

3.8.3 Calorimetry - Effect of Probe Depth

Water (1250 ml) was charged to the vessel. After calibration at 20 °C, the probe was turned on for 10 minutes at power setting 5.0 at depths of 1.0 cm to 7.0 cm in steps of 1.0 cm. The procedure was repeated at power setting 10.0 at depths of 7.0 cm to 1.0 cm in steps of 1.0 cm.

Table 3.17

Heats of Reaction

Probe setting	Probe depth(cm)	Integral(kJ)	Average(W)
5.0	1.0	18.7	31.2
5.0	2.0	18.8	31.3
5.0	3.0	19.1	31.8
5.0	4.0	20.5	34.2
5.0	5.0	22.5	37.5
5.0	6.0	23.0	38.3
5.0	7.0	23.4	39.0
10.0	7.0	61.0	101.7
10.0	6.0	55.7	92.8
10.0	5.0	52.7	87.8
10.0	4.0	51.4	85.7
10.0	3.0	46.5	77.5
10.0	2.0	42.8	71.3
10.0	1.0	42.2	70.3

3.8.4 Calorimetry - Effect of Temperature

Water (1250 ml) was charged to the vessel. After calibration at 20 °C, and using a power setting of 5.0 at a depth of 7.1 cm the probe was turned on for 10 minutes at 10 °C to 70 °C in steps of 10 °C, the reactor was then cooled to 20 °C.

Table 3.18

Heats of Reaction

Temperature(°C)	Integral(kJ)	Average(W)
10	24.9	41.5
20	24.8	41.3
30	25.1	40.2
40	23.9	39.8
50	23.5	39.2
60	21.8	36.3
70	19.5	32.5

3.8.5 Calorimetry - Heat Transfer Coefficient Determination

Water (1250 ml) was charged to the vessel. After calibration at 20 °C, the temperature was increased to 40 °C and the reactor calibrated. The temperature was then increased to 70 °C and calibrated again. The probe was turned on for 10 minutes at power setting 5.0 at a depth of 7.1 cm. The reactor was then cooled to 20 °C and calibrated again.

3.8.6 Comprehensive solvent study

The solvent (1250 ml) was charged to the vessel, and after stabilisation at 20 °C, the reactor was calibrated. The solvents were then sonicated for ten minutes at a power setting of 5, and with the probe immersed to a depth of 7.1 cm.

Table 3.19

Heats of Reaction

Solvent	Integral(kJ)	Average(W)
Water	26.4	44.0
Methanol	22.3	37.1
Ethanol	24.0	40.1
Propan-1-ol	25.1	41.9
Propan-2-ol	24.2	40.3
Butan-1-ol	26.2	43.6
Butan-2-ol	25.4	42.3

iso-Butanol	25.5	42.7
Pentan-1-ol	26.7	44.4
Hexane	19.7	32.8
Cyclohexane	23.1	38.5
Pentane	15.6	26.0
Heptane	21.5	35.8
Decane	23.6	39.3
Benzene	23.8	39.7
o-Xylene	25.4	42.4
m-Xylene	24.6	41.0
p-Xylene	24.1	40.2
Toluene	24.1	40.1
Acetone	20.8	34.6
Butan-2-one	22.6	37.7
Pentan-3-one	23.6	39.3
Cyclohexanone	26.2	43.7
4-Methylpentan-2-one	23.9	39.8
1-Methyl-2-pyrrolidinone	28.1	46.9
Dimethylsulphoxide	28.9	48.2
Acetonitrile	23.0	38.4
Pyrrole	27.4	45.7

3.8.7 Calorimetry - Probe Tip Erosion

The same water was used to determine the probe's output at different depths and at different temperatures. At the end of these experiments the water was drained and filtered to yield 0.1 g of titanium metal (assumed not oxidised) from the probe tip. The diameter of the probe tip is 12 mm which relates to a surface area of 1.13 cm^2 and a metal loss rate of approx 0.02 $g/cm^2/hr$ at an equivalent power setting of 5.0 in water.

4.0 REFERENCES

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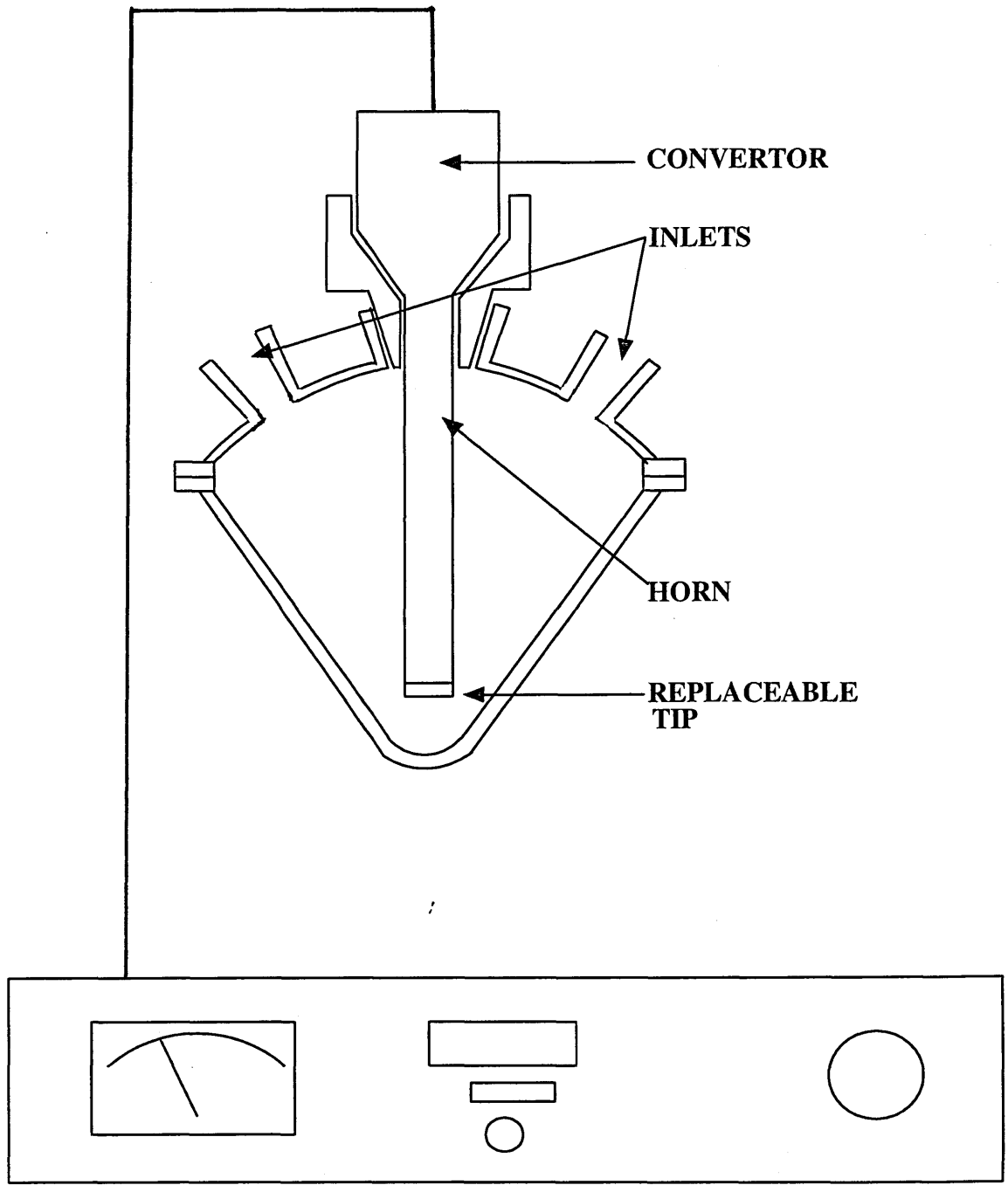
5.0 APPENDICES

APPENDIX 1

ULTRASONIC FLASK



APPENDIX 2

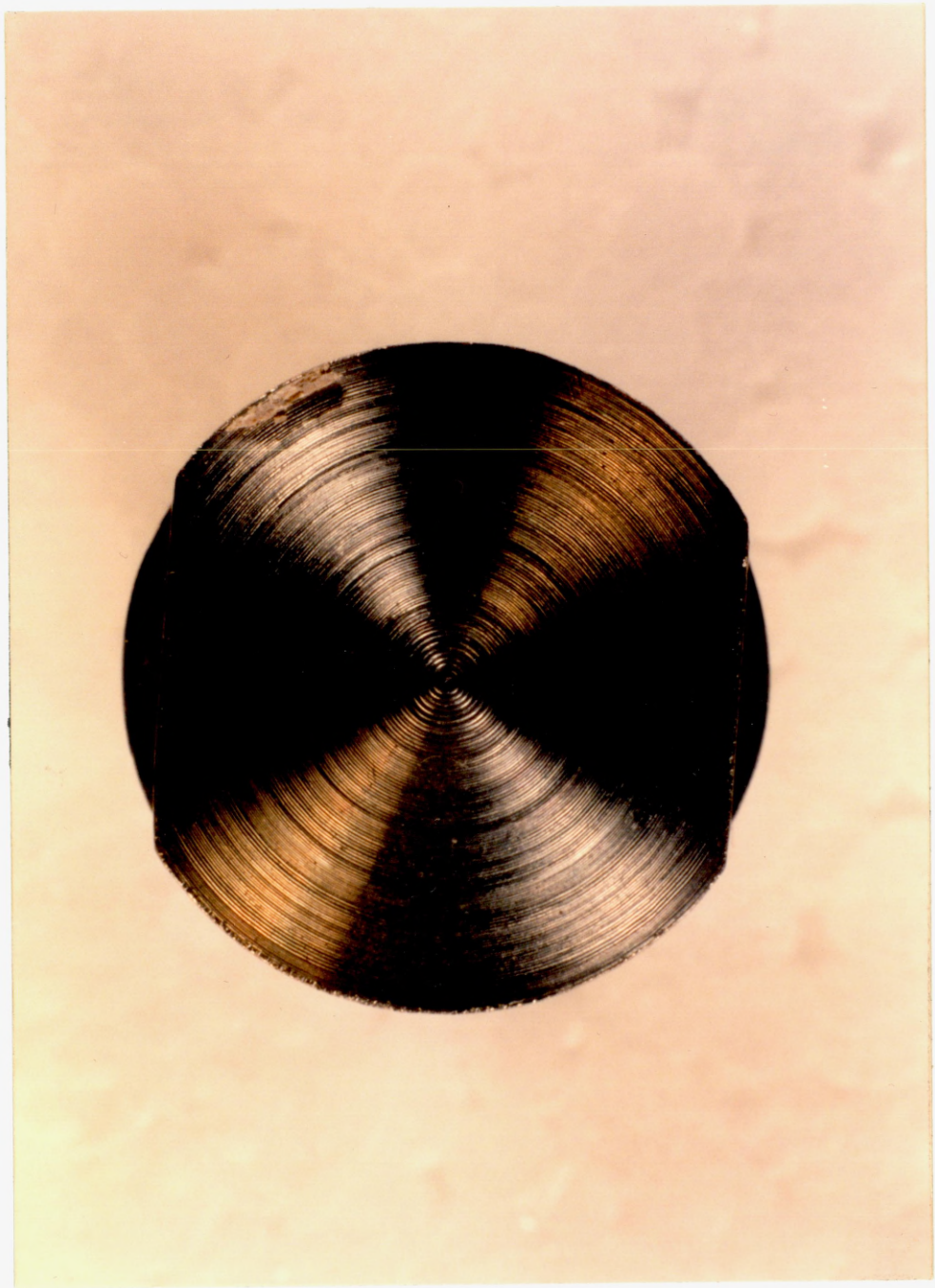
PHYSICAL PROPERTIES OF SOLVENTS

SOLVENTS	BPt (°C)	s.g	Cp (J/gK)
Water	100.0	1.0000	4180
Ethanol	78.5	0.7848	2500
Propan-1-ol	97.5	0.8040	2400
Butan-1-ol	117.5	0.8104	2400
Methanol	64.7	0.7912	2500
Pentan-1-ol	138.5	0.8112	2400
Propan-2-ol	82.5	0.7848	2400
Hexane	69.0	0.6592	2300
Heptane	98.4	0.6840	2300
Decane	174.0	0.7304	2200
Cyclohexane	80.7	0.7792	1800
Benzene	80.1	0.8736	1700
Pentane	36.1	0.6264	2200
o-Xylene	144.0	0.8696	1700
m-Xylene	139.3	0.8680	1700
p-Xylene	138.0	0.8656	1700
Toluene	110.6	0.8672	1700
Cyclohexanone	155.6	0.9472	1800
4-Methylpentan-2-one	117.5	0.8000	2100
Butan-2-one	79.6	0.8048	2250
Pentan-3-one	102.0	0.8528	2100
Acetone	56.0	0.7912	2210
iso-Butanol	108.0	0.7912	2500
Butan-2-ol	98.0	0.7960	2700
1-Methyl-2-pyrrolidinone	81.5	1.0176	2100
Dimethyl sulphoxide	189.0	1.0848	2000
Acetonitrile	82.0	0.7744	2264
Pyrrole	131.0	0.9528	2000
Acetic acid	117.0	1.0336	2280
Thiophene	84.4	1.0573	1500
THF	67.0	0.8890	1718

APPENDIX 3

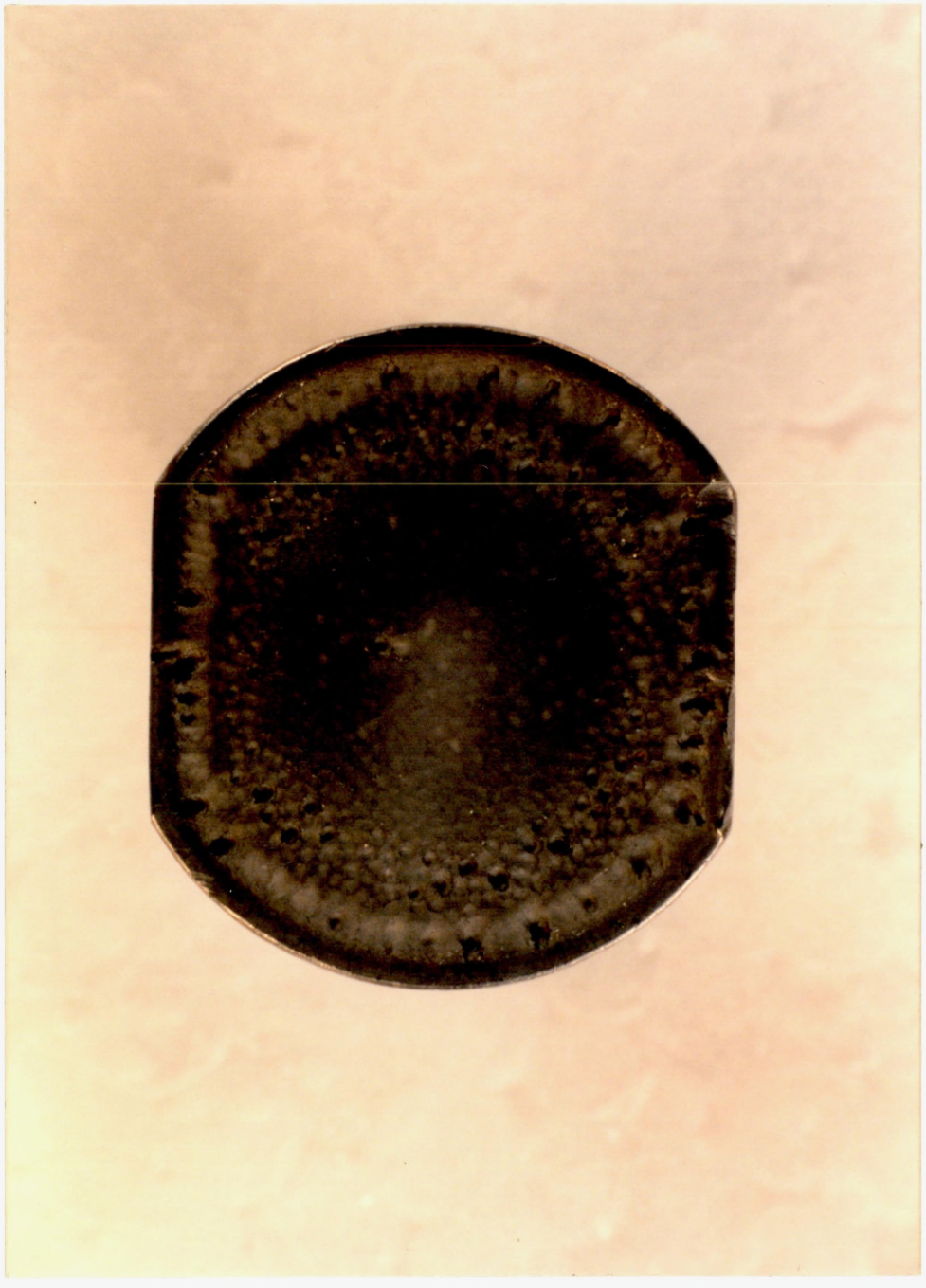
CAVITATION EROSION OF PROBE TIPS

NEW PROBE TIP



APPENDIX 3 CONTINUED

WORN PROBE TIP



APPENDIX 3 CONTINUED

EXCEPTIONALLY WORN PROBE TIP